Early diagnosis of Alzheimer's disease with PET imaging

Student thesis by

Lene Pålhaugen

University of Oslo
Faculty of Medicine

October 2011

Supervisor: Professor Leif Gjerstad

Abstract

Background: Alzheimer's disease (AD) is the most common of the dementia disorders, and age is the main risk factor. In Norway, there are approximately around 60 000 demented persons, and the prevalence is expected to increase more than twofold over the next 40 years. AD is a neurodegenerative disease, and the pathology probably starts many years before the onset of symptoms. Early diagnosis has to an increasingly extent come into focus of AD research. There is the comprehension that drug intervention, when available, should start at an early phase of the disease, before extensive irreversible neuronal damage occurs. Biomarkers of the disease can be measured in vivo, and are associated with specific features of the pathophysiological processes. Cerebral glucose metabolism and amyloid depositions measured by positron emission tomography (PET) are such biomarkers, and the aim of this review is to evaluate these in early Alzheimer's disease. Results from the most important longitudinal PET studies of subjects with mild cognitive impairment are collected and compared, and the ability of baseline PET measurements to predict future conversion to AD or cognitive decline is of special interest.

Methods: Literature study based on non-systematic search in the PubMed database.

Main results: ^{18}F-fluoredeoxyglucose PET measurements are able to predict future AD with accuracies ranging from 56 – 90 %, sensitivities from 57 – 93% and specificities from 47 – 91%. Retention of the amyloid binding ^{11}C-Pittsburgh compound B (PiB) predicts AD with accuracies ranging from 65 – 87 %, sensitivities from 93 – 100 % and specificities from 56 – 81 %. Patterns of glucose hypometabolism and amyloid depositions are rather consistent in the different studies.

Concluding remarks: Some of the longitudinal studies achieved good accuracies and show that AD can be diagnosed in an early phase using PET.

Contents

1 Introduction

Alzheimer's disease (AD) is the most common of the dementia disorders, accounting for more than 70 % of the cases, and age is the main risk factor. In Norway, there are approximately around 60 000 demented persons, and the prevalence is expected to increase more than twofold over the next 40 years (1). The disease is therefore expected to become a major public health concern. The disease is life changing for the individuals affected and their families. Slowly the patients lose their memory and cognitive function, and also their personality change. For the time being, there is no medical therapy that can stop or reverse the neurodegenerative development, but several clinical trials are on-going (2).

At a histopathological level, AD is characterized by the presence of amyloid plaques, neurofibrillary tangles, activated microglia and neuronal cell loss. Macroscopically there is atrophy in certain brain areas including the temporal and frontal lobes, due to degeneration of synapses and neuronal cell death. The diagnosis is not definite until post-mortem neuropathologic assessment is performed and requires the presence of amyloid deposits and neurofibrillary tangles in the hippocampus and neocortex. The pathogenesis is not fully understood, but according to the amyloid cascade hypothesis, the deposition of amyloid β peptides (Aβ) leads to neuronal dysfunction and subsequent death. The Aβ peptides are the results of cleavage of the amyloid precursor protein (APP), which is a transmembrane glycoprotein, into $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$ and Aβ oligomeres. The $A\beta_{1\text{-}42}$ aggregates more easily than $A\beta_{1\text{-}40}$, and is more associated with the disease. The ratio of these two isoforms is a result of the pattern of cleavage of APP by α, β and γ secretases. Amyloid plaques are extracellular deposits of fibrils and amorphous aggregates of Aβ, but also diffuse plaques are present to a large extent. The amyloid cascade hypothesis suggest that toxic levels of Aβ concentration triggers the formation of intracellular tangles of hyperphosphorylated tau protein, but the pathway between plaques and tangles is not clearly understood (3). Also alterations in glial cells are seen.

Aβ is thought to damage synapses and neurites. Especially neuronal circuits involved in learning and memory seem vulnerable to the pathologic processes in AD. There is seen loss of neurons in the entorhinal cortex, hippocampus, frontal, parietal and temporal cortices in AD patients, but this occurs over a time period of many years, and probably starts long before symptoms occur. Genetics is estimated to account for around 70 % of the risk of developing AD, and the most consistently associated risk gene is apolipoprotein E (ApoE). Homozygotes of the ε4 variant are more than 7 times more likely to develop the disease than those with ApoE ε3 alleles (2).

The last decade, early diagnosis of AD has to an increasingly extent come into focus. There is the comprehension that drug intervention, when available, should start at an early phase of the disease, before extensive irreversible neuronal damage occurs. In this context, many research studies have examined the ability of different biomarkers to diagnose AD at different stages of the disease and to monitor disease progression. The biomarkers are parameters that can be measured in vivo, and that are associated with specific features of the pathophysiological processes. Both fluid and imaging measures are included in the term, and most commonly in the AD context are protein levels in cerebrospinal fluid, brain atrophy as measured by structural magnetic resonance imaging (MRI) and glucose hypometabolism and amyloid depositions as measured by positron emission tomography (PET). Very recently, biomarkers were incorporated in the new recommendations on diagnostic

guidelines of the American National Institute on Aging (NIA)(4). Also the pre-dementia stages of AD are included in the new guidelines, reflecting the fact that AD dementia is the end stage of several years of pathological processes and increasing brain damage. The pre-dementia phases include the pre-clinical phase, in which no symptoms have yet occurred, and the mild cognitive impairment (MCI) phase, in which there most often are symptoms of reduced episodic memory and possibly other cognitive functions, but activities of daily living are not affected. The dementia phase is when also activities of daily living are interfered. The recommendations for the pre-clinical phase are intended for research purposes only. Similarly, an international working group revised the research criteria for the diagnosis of AD a few years ago, also incorporating biomarkers as supportive criteria (5). It is emphasized that there is need of further research to validate the application of biomarkers, for instance more biomarker comparison studies, studies on the combination of biomarkers, more post-mortem studies and standardization of criteria defining abnormal and abnormal findings (4).

Several large, longitudinal multi-site studies started some years ago, measuring several biomarkers in the same subjects, in order to get a wider knowledge about such issues. The first project was the Alzheimer's Disease Neuroimaging Initiative in North-America, which started in 2004 and enrolled 1000 volunteers at 59 centers. Standardizing the measurement and imaging techniques has also been one of the goals. Researchers worldwide can apply and get access to the extensive database of biomarker measurements. Later, similar projects were initiated in Australia, Europe, Japan and elsewhere (6).

PET measures emissions from radioactively labeled tracers that have been injected into the bloodstream. Using the radiolabelled glucose analogue ^{18}F-fluorodeoxyglucose (FDG), cerebral glucose metabolism is measured. The variation in uptake of FDG at different regions of the brain supposedly mirrors differences in levels of neurosynaptic activity. It has been shown that specific patterns of hypometabolism is connected to AD pathology (7)

The ^{11}C-labelleled PET tracer Pittsburgh compound B (PiB) seems to bind to fibrillary amyloid β with high affinity, and makes it possible to image amyloid plaques. ^{11}C-PiB is the most widely used amyloid tracer, but the short half-life of only 20 minutes of ^{11}C demands an on-site cyclotron for production of the isotope, and this prevents widespread clinical use. The physical half-life of ^{18}F is 110 minutes, which makes it possible to produce ^{18}F-labelled tracers off-site and ship to the PET-centers. Three such tracers for amyloid imaging are currently being investigated in clinical trials, namely florbetapir, florbetaben and flutemetamol. They are developed as proprietary tracers for commercial distribution (8).

The aim of this review is to evaluate cerebral glucose metabolism and amyloid depositions as biomarkers in early Alzheimer's disease. Results from the most important longitudinal PET studies of MCI subjects are collected and compared, and the ability of baseline PET measurements to predict future conversion to AD or cognitive decline has been of special interests. If additional biomarkers were measured in these studies, those results are also described. In order to rule out a possibly important source of error, also longitudinal studies including post-mortem assessment are reviewed. Such studies can tell whether there is correspondence between imaging findings and actual neuropathology seen in Alzheimer's disease. Finally, the PET methods are briefly compared with MRI methods.

2 Methods

A literature search was done in PubMed. Also the Cochrane database was searched, but only a few irrelevant studies were found. The search design was set up to include articles of PET studies in either AD or MCI patients, and the search was limited to studies performed in humans, to articles written in English and were published after 2004:

("Alzheimer Disease"[Mesh] OR "mild cognitive impairment") AND "Positron-Emission Tomography"[Mesh]

Limits: **Humans, English, Publication Date from 2005/01/01 to 2011/08/30**

This resulted in 635 articles. A primary sorting of these based on their abstracts was performed, based on following exclusion criteria:

- samples of less than 30 subjects in total or less than 20 MCI subjects
- no PET imaging, only MRI or CSF measurements
- emphasis on image processing or evaluation of different statistical methods
- emphasis on monitoring treatment effects
- emphasis on subcategories of AD patients

Then 206 articles remained. In this selection, several sub-searches were performed to find studies involving the different PET tracers like FDG, PiB, florbetapir, florbetaben, flutemetamol or FDDNP. Also searches for “longitudinal” were performed in the different sub-selections. Articles of longitudinal studies published most recently were read first, since these often contained references to other similar studies. If such studies were not in the selection, they were included.

The sub-selection of FDG PET studies was analyzed first. The original idea was to exclude studies with less than 30 MCI subjects, but gradually it became evident that rather few studies would remain for analysis. So this criterion was changed to include studies of more than 25 MCI subjects. In the comparison of post-mortem studies, studies of more than 20 MCI or AD subjects were included, and here also studies going back to year 2000 were included, in order to get a selection of a certain size.

Likewise, the criteria were modified for the analysis of longitudinal PiB PET studies as well. There were even less of these studies, and the inclusion criterion was studies of more than 20 MCI subjects. Post-mortem studies are rare, and most case-studies published were briefly described. For the other 18F-labelled amyloid tracers, there are not published longitudinal studies of MCI subjects. One post-mortem study is published, of florbetapir. For each tracer category, also the largest cross-sectional study with MCI subjects is described, because this gives valuable information about what brain regions are involved for the different PET tracers.

There has been research in the field of FDG PET imaging of AD patients for nearly three decades, and limiting the search selection to studies published after 2004 probably excluded several interesting studies. Nevertheless, it was considered that general inclusion criteria were preferred in order to get a reasonable amount of studies, and one would assume that the later studies benefit from development in image processing and analytical methods. Limiting the number of articles to those

published after 2004 will ensure that longitudinal studies of the larger multi-site projects like ADNI were be included.

3 Results

3.1 PET with ^{18}F-Flurodeoxyglucose

Several studies the last decades have been investigating the pattern and degree of cerebral glucose metabolism reductions in connection with AD pathology at different stages. It has been shown that the uptake of the tracer ^{18}F-fluorodeoxyglucose is significantly reduced in certain brain areas years before the onset of AD symptoms in predisposed individuals, and the extent and topography correlate with symptom severity and predict histopathologic findings (9). The posterior cingulate and the parieto-temporal cortices become early involved, while frontal cortices show reduced glucose metabolism later in the disease progression. Hemispherical asymmetries often occur. The cerebellum, the sensorimotor cortex, thalamus and pons are mainly unaffected (10).

Quite recently, baseline results of the large multi-site study ADNI was published (11). FDG PET images from 82 normal controls, 142 amnestic MCI patients and 74 AD patients were analyzed and compared. Both the AD and MCI group had significantly lower glucose metabolism in precuneus, posterior cingulate and parietotemporal regions, but also the occipital and frontal cortices. Within the normal controls, the ApoE ε4 carriers had lower metabolic rate than non-carriers in bilateral precuneus and left frontal cortex. The ApoE ε4 carriers within the MCI group showed hypometabolism in an extensive region of the right temporal cortex. Small differences were found between the ApoE ε4 carriers and non-carriers within the AD group. They also found that the regional hypometabolism was correlated with the clinical disease severity in terms of CDR and MMSE scores. When analyzing the AD group separately, significant correlations were found between lower MMSE score and lower FDG uptake in the left frontal and temporal cortex, fusiform gyrus and striatum.

3.1.1 Longitudinal FDG PET studies including post-mortem neuropathologic assessment

There are a few longitudinal studies done with follow-up until death and autopsy is performed. From this literature search and another review, five such studies with more than 20 subjects were found (12). The studies are described below, and results are summarized in table **1**.

A large multicenter study by Silverman et al followed 138 patients for a period of 2 to 9 years (13). They underwent clinical evaluation for dementia, FDG-PET scan and neuropathologic examination after death. Due to lack of uniformity of procedures among the contributing sites, standardized clinical rating of dementia severity was only obtained for 79 of the subjects. Of these, 70 % were mildly impaired (questionable or mild dementia) at the time of the initial evaluation. The scan results were classified by two independently working nuclear medicine physicians, blinded to the pathological or clinical information. The classifications of the images as AD positive or negative were concordant in 94 % of the cases. The autopsies took place on average 2.9 years after the PET scan. Ninety-seven had findings which were classified as being positive for AD, and only 8 of these had co-morbid conditions. Twenty-three were positive for other neurodegenerative diseases than AD, including frontotemporal dementia, dementia with Lewy bodies, Creutzfeldt-Jacob disease,

progressive subcortical gliosis, progressive supranuclear palsy and lipofuscinosis. In 18 subjects, no neurodegenerative disease was found.

FDG-PET correctly identified the presence or absence of AD in 88 % of the cases, with a sensitivity of 94 % and a specificity of 73 %. Also a subgroup of 55 patients was analyzed, with questionable or mild dementia at the time of the PET scan. The sensitivity and specificity of FDG-PET was 95 % and 71 % for this subgroup, and the same accuracy was achieved when identifying AD at an earlier stage.

In a study of Foster et al, 45 subjects were studied retrospectively based on clinical summaries and PET scans (14). There were only two groups, consisting of 31 with AD and 14 with FTD. Some co-morbidity was revealed in the neuropathologic assessments. Six neurologists visually rated the FDG PET images after brief training. They knew the diagnosis was either AD or FTD, and though 5 % of the images could be rated as normal, this was not an option. Glucose metabolism was reduced in frontal, anterior cingulate and anterior temporal regions in FTD subjects, and in temporoparietal and posterior cingulate regions in AD subjects. Significant hemispheric asymmetry was seen in approximately half of both AD and FTD cases, and the right hemisphere was more often hypometabolic in the AD subjects. Also clinical summaries were evaluated independently from the PET images. The accuracy of the initial clinical evaluation of 79 % improved to 90 % after considering the PET scans. FDG PET alone correctly classified the subjects with 98 % sensitivity and 73 % specificity.

Jagust et al followed a group of 44 subjects, mostly selected from a university dementia clinic (15). A few were recruited from the community as control subjects. They underwent two clinical evaluations and one FDG PET scan in between. The median time between the initial evaluation and the PET scan was 0.3 years, and between PET scan and autopsy was 3.6 years.

Diagnoses were assessed at multi-disciplinary conferences, and included AD, dementia with Lewy bodies (DLB), frontotemporal lobar degeneration (FTLD), vascular dementia, both AD and vascular dementia, cognitively impairment but not dementia (CIND), normal and unknown condition. FDG-PET scans were categorized as AD or non-AD by two experienced raters, blinded to clinical diagnosis. Done independently they agreed on 73 % of the cases, and consensus ratings were done in those subjects where they differed in diagnostic category. Neuropathologic examinations performed after death verified that the sample was a heterogeneous group. Twenty-five subjects were AD positive (defined by Consortium to Establish a Registry of Alzheimer's Disease - CERAD "definite" or "probable" AD), including six subjects with both cerebrovascular disease and AD. Nineteen were AD negative, but only two were normal. The others were diagnosed with cerebrovascular disease, possible AD, DLB, FTLD, leukoencephalopathy and alcoholic encephalopathy.

FDG-PET predicted the outcomes with a sensitivity of 84 % and specificity of 74 %. This was better than the initial clinical evaluation (sensitivity 76 %; specificity 58%) and at about the same level as the final clinical evaluation which took place almost 4 years later (sensitivity 88 %; specificity 63 %). The positive predictive value of an initial clinical AD diagnosis increased from 70 % to 84 % if also the FDG PET image was interpreted as positive for AD. The negative predictive value increased from 65 % if the diagnosis initially was not AD to 83 % if also the FDG PET image was negative.

In an early study, by Minoshima et al, 10 subjects with AD, 7 subjects with a Lewy body variant of AD and 4 subjects with diffuse Lewy bodies disease (DLBD) were investigated retrospectively (16). Clinically 18 subjects had received a probable AD diagnosis, some with also extrapyramidal signs, and 3 had received a diagnosis of Parkinson's disease. PET images were analyzed by an automated ROI-based method. The autopsy confirmed that AD only patients had metabolic reductions in lateral parietal, temporal and frontal association cortices as well as posterior cingulate cortex. The patients with dementia of Lewy bodies, including those with co-morbid AD, showed significant reduced glucose metabolism in the occipital lobe, and particularly primary visual cortex, but also in the lateral association and posterior cingulate cortices, similar to AD. Based on glucose metabolism in primary visual cortex, FDG PET could distinguish pure AD patients from the DLB patients with sensitivity 90 % and specificity 80 %.

Another early study was described by Hoffman et al (17). It included 22 individuals with memory loss or dementia which was difficult to characterize. They were all patients at a memory clinic, and they were followed up to 7 years. Three of the patients had only biopsy taken and are excluded from the test results calculated here. Nineteen of them eventually underwent an autopsy for a pathologic diagnosis. FDG-PET scans were taken on average 30 months before. The images were visually graded by an experienced nuclear medicine physician, who was blinded for the clinical diagnoses. The final diagnoses included Creutzfeldt-Jacob disease, neuronal degeneration, Lewy body disease, progressive supranuclear palsy, Parkinson's disease and mesio-limbo cortical dementia in addition to AD. By FDG PET images, the subjects were classified as AD or non-AD with a sensitivity of 88 %, specificity of 67 % and overall accuracy of 82 %. The clinical evaluation had the same sensitivity, but a specificity of 100 %. These numbers are derived on a small sample size, and especially the non-AD group is small with only 6 subjects, which limits the statistical confidence of the specificity.

A small study was described recently by Mosconi et al (18). The sample consisted of only 7 subjects, but it is worth mentioning because of its qualitative information. Initially it was four normal subjects and three with mild AD. The follow-up time was long, up to 19 years, and the subjects underwent 2 – 4 PET scans each. The PET images were compared to a reference normal database of 55 normal controls. Two of the subjects with normal status at baseline declined to MCI, and the other two normal subjects declined to AD. In these four initially normal subjects it was possible to detect significant reductions in glucose metabolism in the hippocampus while they still had the diagnostic status as normal and up to 7 years before they received the MCI diagnosis. At that stage, also the parietotemporal and posterior cingulate cortices were involved. AD was then developed one and two years after the MCI diagnosis in two of the initially normal subjects. Glucose hypometabolism in the frontal cortex was only seen in one AD subject. For all subjects the decline in glucose metabolism correlated with dementia severity in life and pathological diagnosis of AD. Those with the clinical MCI diagnosis were classified as possible AD by autopsy (CERAD), one of them also with Parkinson's disease. The patients with clinical diagnosis AD at the last evaluation was confirmed as definite AD (CERAD).

An aggressive and rare variant of AD, early onset familiar AD due to a gene mutation MET146Val PSEN1, was studied in a Swedish-Finnish family by Schöll et al and published recently (19). Only two carriers were followed, but this study anyhow provides some valuable insight. Several PET scans monitored a rapid cognitive deterioration, and eventually post-mortem examinations were done.

Along with clinical decline, as measured with several neuropsychological tests, it was measured increasingly hypometabolism in almost all the predefined ROIs, especially posterior cingulate, parietal and parietotemporal cortices. The levels were significantly lower than the mean of an AD reference group. Similarly, the quantitative levels of neurofibrillary tangles and neuritic plaques were significantly higher in these two subjects at post-mortem examination compared to brain tissue of AD patients from a brain bank. The FDG uptake values at the last PET scans, taken 4 and 5 years before death, correlated significantly with the amount of neuritic plaques in corresponding brain areas, but not with neurofibrillary tangles.

In table 1, the capability of FDG PET as a diagnostic test for AD in some of the abovementioned studies is summarized.

Table 1. *Results from longitudinal FDG PET studies with autopsy as gold standard.*

Study	**N**	**Pathologic diagnosis**	**Time from PET to autopsy (years)**	**Method**	**Sens./spec.; PPV/NPV; Accuracy (%)**
Silverman 2001 (13)	138	97 AD 41 non-AD	2.9	FDG-PET images: Visually rated by two experienced raters Pathology: criteria varied between sites	94/73; 89/83; 88
Foster 2007 (14)	45	31 AD 14 FTD	6.2	FDG-PET images: Visually rated by 6 neurologists with brief training Pathology: NIA-Reagan	98/73; 88/91; 89
Jagust 2007 (15)	44	25 AD 19 non-AD	3.6	FDG-PET images: Visually rated by two experienced raters Pathology: CERAD and NIA-Reagan	84/74; 81/78; 80
Minoshima 2001 (16)	21	10 AD 7 AD + DLB 4 DLBD	3.2	PET: automated 3D-sterotactiv surface projection, 12 predefined ROIs, normalized to pons. Uptake in primary visual cortex as discriminator. Pathology: Kachaturian, Lewy bodies	90/80; 82/90; 86 (for DLB and DLBD)
Hoffman 2000 (17)	19	13 AD 6 non-AD	2.5	FDG-PET images: Visually rated by one experienced rater Pathology: CERAD	85/67; 85/67; 79

CERAD: Consortium to Establish a Registry for Alzheimer's Disease;
NIA-Reagan: National Institute on Aging – Reagan Institute Criteria

The sample in the study by Silverman et al is large in size, includes a heterogeneous group of dementia diseases, and most of the patients had dementia at a mild stage at the time of FDG PET scan. This study is thus the most interesting, and the sample size makes the estimated diagnostic values statistically meaningful. The 95 % confidence interval of the sensitivity was 89 – 99 %, and for the specificity it was 60 – 87 %.

Also Jagust et al and Hoffman et al diagnosed AD in heterogeneous groups, with several different dementia diseases and co-morbid conditions. The former study is also of a certain size, and the results are interesting and comparable with the study of Silverman. Worth mentioning is the fact that FDG PET provided the same diagnostic accuracy as clinical diagnosis 4 years later. It was also shown a substantial increase in positive and negative predictive values when FDG PET was added to the clinical evaluation, which is more likely to be the clinical context. The sensitivity of FDG PET was not within the confidence interval of the results by Silverman et al, and this could be explained by the visual evaluations of the raters of PET images or differences in sample size and composition.

In the study of Foster et al there were only AD and FTD patients, and this was known by the neurologists assessing the PET images. The diagnostic values are still of some interest because also in the other studies, the outcome was AD or not AD. The 95 % confidence intervals were 94 – 100 % and 57 – 82 % for sensitivity and specificity, respectively.

The studies of Minoshima et al and Hoffman et al are small and thus the diagnostic performances are of less general interest. Minoshima et al included co-morbid AD and DLB in the non-AD group, while in Silverman et al, Jagust et al and Hoffman et al AD co-morbid conditions were included in the AD group, when sensitivity and specificity were calculated.

The study of Mosconi et al with multiple FDG PET scans and clinical evaluations provides valuable information of the connection between clinical symptoms, actual brain damage as visualized by FDG PET and at last verified by autopsy. It was seen that FDG PET images could show reduced glucose metabolism in the hippocampus several years before symptoms onset, and that at the MCI stage also parietotemporal and posterior cingulate cortices were involved. At the stage of AD, the frontal cortex could be affected.

In general, the sensitivity is good and most AD patients could be correctly diagnosed using FDG PET at an early state. But due to a poorer specificity, several patients would incorrectly be diagnosed with AD, but in reality have other dementia diseases or in fact be cognitively normal (2/18 in Silverman et al).

3.1.2 Longitudinal FDG PET studies of MCI subjects

Most studies including more than 25 subjects are reviewed. The largest longitudinal study is within the ADNI project. Initially the major goal of the PET component of ADNI was to show that FDG-PET could serve as an outcome measure to track a drug effect with greater statistical power than routine clinical measures. A total of 404 subjects underwent FDG-PET scan at baseline, 368 after one year and 283 after 2 years. Most of the MCI subjects were PET scanned at 1.5 and 3 years as well (20). Several laboratories have analyzed the FDG-PET data, with different approaches.

One study was performed by Landau et al on a subset of the ADNI sample (21). It included 85 MCI subjects who agreed to participate in all biomarker testing, which were FDG PET and structural MRI scans, CSF and blood samples and neuropsychological testing. The goal was to evaluate and compare the prognostic ability of glucose hypometabolism, hippocampal hypertrophy, CSF protein levels, APOE ε4 allele frequency and episodic memory performance, as measured by the Auditory Verbal Learning Test (AVLT). ROI-based data analysis was performed on the FDG-PET data, normalising the tracer uptake in these regions with a reference region comprised of cerebellar vermis and pons

The same kind of data from the other two ADNI subject groups, normal and AD, were used to establish the cut-off values for normal or abnormal measures. They were derived by performing Receiver Operator Characteristics (ROC) analyses optimizing on sensitivity and specificity. Then the cut-offs were used to categorize the MCI subjects as AD+ or AD- on each measure. The actual change of subject status from MCI to AD was established at the recruitment sites and reviewed centrally, and none of the parameters in the analysis of predictors were used as indicators of conversion. During the follow-up period of approximately 2 years, 28 of the 85 MCI patients converted to AD, with an annual rate of 17.2 %. None of the subjects converted to normal status or dementia of another type.

In table 2 the performance of the different biomarkers as diagnostic tests on MCI subjects are listed. The FDG PET results are also listed in table 3 for comparison with other FDG PET studies. Knowing the number of converters versus non-converters, the positive (PPV) and negative predictive values (NPV), and the number of test positives and negatives for the different biomarkers, it is possible to derive sensitivities, specificities and accuracies. In the research article text, positive predictive value is defined as "the number of MCI converters correctly classified as AD+ divided by all the MCI converters", which in fact is the definition of sensitivity. Likewise, the negative predictive value is incorrectly defined as specificity. It is assumed that this is just a textual error, and that the positive and negative predictive values are correctly calculated. The other alternative would that these values in fact are the sensitivity and specificity, but then the 2-times-2 tables would not be coherent, which supports the first assumption. But this slightly reduces the trustworthiness of the numbers.

Table 2. *Test performance of predicting AD conversion in MCI patients for the different biomarkers in the study of Landau et al (21).*

	FDG-PET glucose metabolism	**MRI hippocampal volume**	**CSF $A\beta_{1-42}$**	**AVLT episodic memory**	**ApoE ε4**
PPV (%) *	41	41	38	41	40
NPV (%) *	79	78	76	88	74
Test positive subjects **	51	49	56	61	42
Test negative subjects **	34	36	29	24	43
Sensitivity (%)	75	71	75	89	61
Specificity (%)	47	49	39	37	56
Accuracy (%)	56	56	51	54	58

*From table 2 in Landau et al [34].

** From table e-1 in supplements of Landau et al, available at www.neurology.org.

The episodic memory test score (AVLT) is by far the most sensitive in predicting conversion to AD in the MCI subjects, but the best accuracy was in fact achieved by the ApoE ε4 carrier status. FDG PET was more sensitive than hippocampal volume measurements, but the accuracy was the same.

By using Cox proportional hazard models to evaluate prediction, the authors found that only FDG-PET and AVLT was significant as predictors of conversion in a multivariate analysis, with hazard ratios of 2.72 and 4.30 respectively. Combined hazard ratio was 11.7, which means that the subjects who were positive for both FDG-PET and AVLT had an almost 12 times higher risk of converting to AD than those who were negative on both.

In a mixed effect model, only CSF p-tau$_{181p}$/Aβ_{1-42} ratio significantly predicted cognitive decline as measured by ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive Subscale) in multivariate analysis. It would have been interesting to compare this CSF ratio with the other biomarkers in table 2, but this was not measured in all the MCI subjects, and the portion of converters and non-converters for this MCI subgroup is not stated in the article or its supplements. Thus, the sensitivity, specificity and accuracy of CSF p-tau$_{181p}$/Aβ_{1-42} ratio are unfortunately not possible to derive.

The same research group also compared FDG-PET images and clinical status measured by the Functional Activities Questionnaire (FAQ) and ADAS-cog (22). The sample included approximately 400 subjects in all three categories normal, MCI and AD subjects. They used continuous measures as predictors and outcome variables, rather than conversion/non-conversion status. Here it was found that both low baseline glucose metabolism and a longitudinal decline are sensitive to a decline of the ADAS-cog and FAQ score.

Another research group also used a subset of the ADNI data to analyze the ability of structural MRI, FDG-PET and CSF proteins to predict future cognitive decline in MCI subjects (23). Walhovd et al analyzed data from baseline and the 2-year follow-up measurements in 36 normal controls, 51 MCI subjects and 25 AD patients. Values for grey matter thickness and glucose metabolism in 10 predefined ROIs were calculated, in which effects of age and sex were regressed out. The PET activity in each ROI was normalized to the activity in pons. Baseline values from selected ROIs of MRI and FDG-PET were correlated with the changes in scores in MMSE, CDR-SB and a logic memory test (Wechsler Memory Scale – Revised) two years later. They found significant correlations between

- baseline retrosplenial glucose metabolism (PET) and change in MMSE score
- baseline retrosplenial thickness (MRI) and CDR-SB change,
- baseline retrosplenial thickness (MRI) and MMSE,
- baseline hippocampal volume (MRI) and change in WMS-R score, and
- baseline entorhinal glucose metabolism (PET) and change in MMSE score,

in that order. They found no significant correlation between the CSF proteins ratio t-tau/Aβ42 and any of the clinical change measures, which in that respect is not in accordance with the previously described ADNI results by Landau et al [34]. This analysis did not include any rate of conversion from MCI to AD during the two-year follow up and predictive capability in that respect.

A third approach was taken in analysis of the longitudinal FDG PET data of ADNI. Herholz et al used a fully automated voxel based method to calculate PET scores of the images of 44 normal controls, 94 MCI subjects and 40 patients with mild AD, which had all undergone four PET scans during a two-year follow-up period (24). Thirty MCI subjects had converted to AD after two year. Also, seven MCI subjects reverted to a status as cognitively normal. Two of the control subjects progressed to MCI status. Abnormal PET score at baseline predicted conversion to a more severe diagnostic category

with sensitivity 57 % and specificity 67 %.The positive and negative predictive values were 45 % and 77 %, respectively. This is lower sensitivity than what Landau et al got, but a higher specificity and accuracy (21).

Mosconi et al reported a large longitudinal study following 77 initially normal subjects for a period averaging 9 years (25). At study end, 19 had declined to MCI, 6 were diagnosed AD and 5 had progressed to other dementia diseases. The decline to MCI and AD took place on average 8 years after baseline examination. All the six subjects who declined to AD received the MCI diagnosis after an average of 3 years after baseline. Both a ROI method with hippocampus and PCC and a voxel-based analysis of the entire brain was used. Only hippocampal glucose metabolism was found to predict future cognitive decline in the normal subjects. At baseline the hippocampus metabolic rate was reduced 15 % in those who declined to MCI and 26 % in those who eventually were diagnosed AD. It was 13 % lower in those who declined to a non-AD dementia. This indicates that hippocampal FDG-PET measures are sensitive to identify normal elderly at risk for cognitive decline.

Anchisi et al followed 48 amnestic MCI subjects over a relatively short time period, and the results are summarized in table 3 (26). An important finding was that if the PET scan was not defined as abnormal, which meant regional uptake value ratio below a derived cut-off, the chance of converting to AD within the first year was only 3%.Those who converted within one year showed significant hypometabolism in the parietal and posterior cingulate cortex. Also, combining FDG PET and a verbal recall test (California Verbal Learning Test – Long Delay Free Recall), it was possible to enhance the prediction accuracy to 94 % compared to 85 % using FDG PET alone. Especially the specificity and positive predictive value were improved, to 97 % and 92 %, respectively, but on the expense of the sensitivity and negative predictive value, which were 86 % and 94 %, respectively.

This effect was not seen in the study of Nobili et al, where the combination of FDG PET and tests of verbal episodic memory did not add any gain to the prediction of MCI subjects converting to AD compared to using only FDG PET (27). The results are listed in table 3. All MCI patients showed reduced glucose metabolism in the bilateral posterior cingulate cortex, left temporal pole and bilateral orbitofrontal cortex. The AD converters also had significantly less FDG uptake in the left lateral frontal cortex compared to the non-converters.

Drzezga et al combined FDG PET results and ApoE ε4 genotype information from 30 MCI subjects, of whom 57 % were carriers (28). It was possible to achieve 100 % sensitivity in diagnosing AD based on baseline measurements, if test positivity was defined as either having abnormal FDG PET or an ApoE ε4 allele. Specificity was rather poor however, of 44 %. If being test positive meant both having abnormal PET scan and being ε4 gene carrier, the subjects were diagnosed with 100 % specificity and 67 % sensitivity. The overall accuracies in these two approaches were reduced compared to FDG PET alone. Results of FDG PET alone are summarized in table 3.

Looking more thoroughly into the MCI non-converters, Pagani et al divided this group into stable and declining MCI subjects (29). Of the initially 29 MCI subjects, 19 remained within that diagnostic category after an average follow-up period of about 20 months. Based on results from episodic memory tests, 9 were shown to be stable MCI subjects while 10 were declining in episodic memory. Their hypothesis was that of the 10 declining MCI subjects there are probably several late converters. PET images were analyzed by a voxel based method, and the three MCI subgroups were compared

with each other and images of 14 elderly controls. The MCI subjects that declined in episodic memory showed hypometabolism in the left hippocampus compared to the normal controls and the stable MCI subjects. The AD converters showed hypometabolism in the bilateral posterior cingulate cortex, the left parietal precuneus and the left fusiform gyrus compared to the controls. There was no significant difference between the control group and the stable MCI subgroup. And the MCI decliners showed no significant difference in glucose metabolism compared to the MCI subjects that converted to AD.

Subcategories of MCI subjects have been studied longitudinally with FDG PET and clinical evaluations by Clerici et al (30). Fourteen amnestic MCI and 12 single domain non-amnestic MCI were followed up to 40 months. In the aMCI group, one remained MCI during the follow-up period, 12 converted to AD and one converted to LBD. In the snaMCI group, 3 subjects remained MCI, 3 converted to AD, 5 converted to LBD and one to FTD. On average, the subjects received their dementia diagnosis 28 months after the MCI diagnosis. Both groups showed significant hypometabolism in PCC, precuneus, the lingual gyri and frontal and temporal cortices compared to normal controls. When the two MCI groups were compared with each other, the aMCI group had a significantly lower metabolism in the left MTL, including the left hippocampus and fusiform gyrus.

MCI subjects subcategorized into early- and late-onset MCI were followed for 5 years by Kim et al (31). Seven of the 12 early-onset and 8 of the 14 late-onset MCI subjects converted to AD within the follow-up period, which gave approximately the same conversion rate of 57-58 %. The converters overall showed significant hypometabolism in posterior cingulate gyrus and frontal and temporoparietal areas compared to the controls. They also obtained significantly lower scores on a delayed verbal recall test. The early-onset converters showed significantly reduced metabolism in the left frontal areas compared to the non-converters. The same difference was seen among the late-onset converters, but it was not significant.

In table 3 the results from some of the longitudinal studies of MCI subjects are summarized. The table includes studies with emphasis on predicting conversion to AD by using FDG PET. The table is based on table 1 in (10), but all the content is reviewed and some information is added and edited compared to the original table.

Table 3. *Summarized results of FDG PET studies of MCI subjects converting to AD.*

Study	N	Age ± SD	M/F	Entry diag-nosis; Mean MMSE score	Average follow-up time (months)	Con-vert-ers; Ann ual rate (%)	Sens./spec.; PPV/NPV; Accuracy (%)	Data analysis	Image scaling	Discri-minating brain area
Herholz 2011 (24) *	94	75 ± 8	66/28	aMCI 27	24	32; 16	57/67; 45/77; 64	Automated VBA (PALZ/PMOD software package)	Global	Temporal and parietal lobes
Landau 2010 (21) *	85	78 ± 7	56/29	aMCI; 27	23	33; 17	75/47; 41/79; 56	1 composite pre-defined ROI /ROC analysis /SPM5	Pons and cere-bellar vermis	Bilateral angular gyri, bilateral PCC and left middle/in-ferior temporal gyrus
Anchisi 2005 (26)	48	67 ± 8	25/23	aMCI; 28	12 (median)	29; 29	93/82; 68/97; 85	SPM99/3 volumes of interest/ROC analysis	Sensori-motor cortex	Parietal cortex and PCC
Nobili 2008 (27)	33	76 ± 5	13/20	aMCI ; 27	21	33; 19	82/91; 82/91; 88	2x25 predefined volumetric ROIs /Principal component analysis /Computerize d Brain Atlas	Global	Bilateral PCC, left temporal pole and left lateral frontal cortex
Drzezga 2005 (28)	30	70 ± 8	14/16	5 aMCI, 25 md-aMCI; 27	16	40; 30	92/89; 85/94; 90	Neurostat/ 20 predefined ROIs/ROC analysis	Not specified	PCC and temporopari etal cortex

* ADNI studies with probable sample overlap.

The accuracy ranges from 56 – 90 %, the sensitivity from 57 – 93 % and specificity from 47 – 91 %. The least interesting parameter may be the positive predictive value. PPV is directly proportional to the prevalence of the disease, and in these research samples the prevalence is higher than in the normal population. A quantitative review found that annual AD conversion rate in MCI subjects is about 4 % in the community population and about 7 % in specialist settings (32). In table 3, the annual conversion rate ranges from 17 to 30 %, and thus the PPVs are artificially high. The NPV are in

these studies between 79 and 97 %, and would probably be high in the community population as well.

The study of Herholz et al and Landau et al involves the largest number of MCI subjects and the longest follow-up period, and presumably therefore are the most trustworthy. But they also got the poorest results, with lower sensitivity, specificity and accuracy than the other studies. Herholz et al achieved better results than Landau et al, using a fully automated voxelbased method, even though these samples probably contain mostly the same subjects. The fact that ApoE ε4 allele carrier status provides the best test accuracy in Landau et al raises the question whether the analytical methods that were used were optimal. The cut-off value of FDG uptake ratio classifying subjects as FDG PET positive or negative were based on analysis of AD patients and normal controls in the study of Landau et al. In the studies of Anchisi et al, Nobili et al and Drzezga et al the cut-off value was determined based on data of the MCI subjects and normal controls, and maybe this partly explains the differences in accuracy, sensitivity and specificity.

Even though average MMSE scores at baseline are comparable for the different studies, of 27-28 points, there is a greater variation between the converters and non-converters in the study of Drzezga et al and Anchisi et al, of almost 2 points. In Landau et al and Nobili et al, there is an MMSE score difference of less than 1 point. Also having the highest annual conversion rates, Drzezga et al and Anchisi et al seem to have more subjects with more severe MCI in their samples, in which future AD probably is more evident. And the best results were achieved by Drzezga et al, with an accuracy of as much as 90 %. Nobili et al got a strong result in a sample population with annual conversion rate in the lower range and MMSE score difference of only 0.2 points between converters and non-converters. They took a different approach in the image processing and statistical analysis, but it is hard to say whether that is a main factor in achieving the high prediction accuracy or not.

The ADNI studies are unique in the sense that multiple methods of measuring possible AD pathology have been used in the same patients and several times over a time period, and thus provide a good way of comparing these methods in the sense of predicting Alzheimer's disease early. Of the studies described here, only Landau et al and Walhovd et al included MRI measurements and CSF sampling in their studies (21;23). As seen from table 2, MRI was slightly less sensitive, a little more specific and just as accurate as FDG PET in predicting future conversion to AD in MCI subjects in the study of Landau et al. In multivariate analysis, only the episodic memory test and FDG PET were the significant variables regarding AD prediction, while the CSF ratio p-tau$_{181p}$/Aβ_{1-42} were the only significant predictor of cognitive decline as measured by ADAS-Cog. Also Walhovd et al found in their study, that retrosplenial metabolism measured by FDG PET showed the strongest correlation with cognitive decline, but also MRI measurements of retrosplenial thickness and hippocampal volume in MCI subjects showed significant correlations (23). It was not found any significant correlation between CSF protein levels and clinical deterioration, as Landau et al did. In the latter article, inconsistencies among studies in general are suggested to be due to methodological issues like image analysis techniques, statistical methods, different cut-off criteria and study designs. Another factor could be differences in the samples, for instance in the degree of cognitive impairment and rate of cognitive decline. Assuming there must be considerable sample overlap in these two studies, this is probably not an issue in this case.

Both Landau et al and Anchisi et al were able to enhance the AD prediction accuracy in MCI subjects by combining FDG PET and episodic memory test, while Nobili et al found no such effect (21;26;27). Pagani et al used episodic memory testing in order to classify a subgroup of the MCI non-converters as decliners, with the hypothesis that these subjects were slow converters (29).

Only in the latter study of Landau et al, Herholz et al and Mosconi et al it was performed FDG PET scans also at follow-ups, and thus measuring the rate of change in glucose metabolism in MCI subjects (22;24;25). Herholz et al found a close correlation in the change in glucose metabolism and cognitive decline as measured by ADAS-cog, especially in the progressing MCI subjects. They also saw that there were 3 times higher variability in the ADAS-cog changes compared to FDG PET changes, and thus FDG PET thus would be a better parameter to measure cognitive decline in clinical trials. Landau et al found similar results, and also observed that there was a significant difference in the glucose metabolism decline in the medial temporal lobe and marginally in the posterior cingulate cortex in MCI subjects compared to normal controls. There was a greater annual rate of hippocampal FDG uptake reductions in the normal subjects that declined to MCI or AD compared to those that remained cognitively normal, in the study of Mosconi et al. This was also seen in the posterior cingulate cortex, but the difference was not significant between those who converted to MCI and those who remained normal.

Reduced hippocampal metabolism was found to predict future development of AD in cognitively healthy subjects (25). Hippocampal hypometabolism was also seen in MCI subjects that did not convert to AD but were declining cognitively (29). These two studies by Mosconi et al and Pagani et al might point to hippocampal hypometabolism as an early predictor of AD. In the MCI subjects converting to AD within a few years, there is found hypometabolism in the posterior cingulate cortex, temporoparietal areas, and sometimes also in lateral frontal and orbitofrontal cortex.

3.2 PET with ^{11}C-Pittsburgh compound B

^{11}C-Pittsburgh compound B (PiB) is an analogue of thioflavin-T, an established histological stain for detecting β amyloid plaques. The hypothesis is that PiB PET images visualizes the fibrillar amyloid plaque in vivo, and this tracer is one of several developed for so-called amyloid imaging, and the most widely studied (33).

In AD patients, increased PiB retention has been found in regions including the frontal cortex, anterior and posterior cingulate cortices, precuneus and striatum, while subcortical white matter, pons and cerebellum are relatively spared. Also a considerable amount of healthy controls show elevated PiB binding, between 20 and 30 % (33). Results are inconsistent whether these subjects show subtle signs of cognitive impairment or not, compared to those without increased levels. In many studies, cut-off values of PIB uptake are established, and PiB PET images are defined as positive or negative, in the sense of increased levels of amyloid plaques or not. How these cut-off values are calculated varies, and no consensus has been reached on what is an abnormal level of PiB uptake (33) . In a recent review, data from several research groups are combined and show that 96 % of 341 clinically diagnosed AD patients, 59 % of 272 MCI subjects and 24 % of 651 cognitively healthy controls were PiB PET positive (34). PiB positivity is more common in ApoE ε4 carriers, compared to non-carriers (35).

The largest PiB PET study to date recently reported their findings at baseline (36). The Australian arm of the ADNI, called Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging performed PiB scans in 177 healthy controls, 57 MCI subjects and 53 mild AD patient. Also MRI images were taken in order to calculate hippocampal, grey matter and ventricular volumes. Clinical and neuropsychological evaluations were done, including a battery of tests. Images were analyzed by ROI based method, and PIB uptake values in the frontal, superior parietal, lateral temporal, lateral occipital and anterior and posterior cingulate regions were averaged. Cut-off values defining abnormal measurements were established for hippocampal volume and PiB retention values. The healthy controls were not representative of the general population, because a higher number of ApoE ε4 carriers were selected. That gave a percentage of 43 %, which is about twice the normal prevalence. Among the MCI and AD subjects, 55 % and 69 % were ApoE ε4 carriers, respectively.

The neocortical PiB binding was higher in the AD than in the MCI group, which again was higher compared to the normal controls. High PiB retention was found in 33 %, 68 % and 98 % of the healthy controls, MCI subjects and AD patients, respectively, and the uptake level differed significantly between the subject groups. In the healthy controls, PiB binding increased with age. There was no significant difference in memory scores between PiB positive and negative healthy controls. PiB binding was significantly greater in ApoE ε4 carriers in the healthy controls and MCI groups. In the AD subjects, PiB binding was greatest in the orbitofrontal and posterior cingulate cortices, precuneus, lateral temporal cortex and striatum, and the same pattern was seen in the healthy controls, but with less involvement of posterior cingulate cortex and precuneus. Hippocampal volume correlated with PiB binding in the MCI subjects and weakly in normal controls, also after non-partial volume correction of PET images, but not in the AD patients. Doing a voxelbased analysis on non-demented sub-groups (healthy controls and MCI subjects), it was found that both hippocampal grey matter volume and temporal PiB binding correlated with episodic memory deficits, and that these two parameters contributed independently (37).

3.2.1 Longitudinal PiB PET studies including post-mortem neuropathologic assessment

There are very few studies of people with both PiB PET imaging and neuropathologic assessment. Most of them are case studies, and none of them would be described here with the inclusion criteria of 20 subjects or more. Nevertheless, the few case reports and small studies are described below since they have some qualitative information about the association between PiB uptake and β amyloid aggregation

The largest study reported so far, by Sojkova et al, was of one demented and 5 non-demented participants from the Neuroimaging Substudy of the Baltimore Longitudinal Study of Aging (38). At the time of the initial imaging, all the participants were clinically evaluated as free of dementia or MCI, but one of them had a CDR-SB score of 0.5 and another of 2.0. The latter subject progressed to a CDR-SB score of 4.5 and had 3 PiB images taken during the follow-up period. PET images were analyzed by ROI based method of 15 predefined regions in addition to cerebellum and 3 regions used in CERAD assessment. The uptake values were highest in the precuneus and posterior cingulate region in 5 of the subjects and in the superior frontal region in the remaining person. The neuropathologic examination took place from 2 months till more than 2 years after PET imaging were done. In two of the patients, there was good agreement between the PiB binding and the postmortem assessment. That was in one subject with negative PiB image and no neuritic plaques,

which is the finding taken into account in the CERAD criteria, and in the demented subject with high PiB uptake and moderate neuritic plaques. Setting the cut-off of PiB uptake ratio to 1.2, also two more of the subjects had PET images in agreement with the neuropathologic findings of moderate neuritic plaques. One of the last two subjects had a high uptake ratio in precuneus, and also the mean value of 8 selected cortical regions was high, but only sparse neuritic plaques were found. Precuneus is not one of the regions examined according to CERAD criteria, but further investigation revealed high amount of Aβ load in precuneus and many diffuse plaques. Also vascular Aβ was found in this subject, and may have contributed to the elevated PiB binding. In the last subject the PET image was not PiB positive, but the neuropathologic examination showed moderate neuritic plaques. One possible explanation might be that there is a polymorphic Aβ, to which PiB does not bind. Another explanation could be the time lag of 2.4 years from the PET scan was taken and till the autopsy was performed.

A patient diagnosed with mild DAT, had elevated total and phosphorylated tau_{181} and reduced $A\beta_{1\text{-}42}$ level in CSF, but one year prior to receiving the diagnosis, he underwent a PiB PET scan which was normal (39). Neuropathologic examination was done 2.5 years after the PiB PET scan. He had enough diffuse plaques to meet the Khachaturian criteria of AD, but the amount of neuritic plaques and tangles only sufficient for the CERAD criteria of "possible AD". The authors of the case report raised the notion that since PiB binds poorly to amorphous cortical Aβ plaques, AD variants characterized by mainly diffuse plaques without substantial amount of fibrillar Aβ, will not be detected by PiB PET imaging. These patients may not receive the AD diagnosis from neuropathologic assessment either, depending on which neuropathologic criteria that are being used.

Another case report described the findings from a 64-year-old patient with severe AD (40). PiB scan was taken 10 months prior to death, and the neuropathologic examination confirmed the diagnosis as "definite AD", according to CERAD criteria. Samples of cortical brain tissue were collected and the Aβ level determined. It was found strong association with the corresponding ROIs showing elevated PiB uptake in the PET image.

The first reported pathologic examination compared with PiB PET images was of a 76-year-old man with a clinical diagnosis of dementia with Lewy bodies (41). He underwent FDG and PiB PET scans about 2 years and 3 months prior to death, respectively. The FDG image showed reduced glucose metabolism in both temporal and parietal cortices and mild reduction in the left frontal lobe. The PiB image showed elevated binding in the posterior cingulate, precuneus, posterior parietal, middle and inferior temporal, insular, and lateral and orbital frontal cortices. He then had MMSE score of 25 and CDR of 1.0. The neuropathologic examination confirmed the diagnosis of dementia with Lewy bodies. Also findings characteristic of AD was found. There was moderate numbers of neurofibrillary tangles and amyloid β pathology, with severe cerebral amyloid angiopathy and moderate diffuse plaques. The overall frequency of plaques was low and met the CERAD criteria of "possible AD". A possible conclusion was therefore that the PiB uptake in this case reflected the Aβ in cerebral vessels more than in the brain parenchyma. PiB does not bind to Lewy bodies or neurofibrillary tangles. Based on this case study, the question was raised that PiB retention does not only occur in AD patients, but also in elderly cognitively normal subjects with raised Aβ and at risk of developing AD, in MCI subjects, in subjects with cerebral amyloid angiopathy and patients with dementia of Lewy bodies with amyloid pathology.

3.2.2 Longitudinal PiB PET studies of MCI subjects

There are only a few longitudinal studies in MCI subjects with PIB PET reported so far, and in most of them the follow-up period has been two years or less. The ability to predict AD conversion is summarized in table 4.

Recently the first longitudinal results from the AIBL study in Australia were published, by Villemagne et al (42). It is the largest longitudinal PiB PET study of MCI subjects so far. At the first follow-up at 20 months after baseline, 106 healthy controls, 65 MCI subjects and 35 DAT subjects were clinically reassessed, and 90 % of them also underwent a second PiB PET scan. These images were analyzed by ROI-based method, and a standardized uptake value (SUV) was calculated for each region, averaged across both hemispheres. Dividing with the cerebellar cortex SUV gave SUV ratios (SUVRs). A neocortical SUVR was calculated as the average of area-weighted mean of frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions. Hierarchical cluster analysis was used to derive a cut-off value of 1.5 for the neocortical SUVR as abnormal versus normal. Of the MCI group, 48 % had developed AD at 20-month follow-up, and another 6 % had developed other types of dementia. The converters showed significantly lower MMSE score, lower episodic memory scores, higher prevalence of ApoE ε4 carriers and higher PiB SUVR at baseline than non-converters. The ability of baseline PiB PET to predict AD conversion is summarized in table 4. Also, five healthy controls developed MCI and one developed AD during the first 20 months after baseline, of whom five had high PiB initially. The MCI and AD groups showed small but significant increase in PiB retention. A greater increase was seen in the milder AD patients compared to those with more severe dementia. Also PiB positive healthy subjects showed a significant increase in PiB uptake. Seeing the three groups as one sample, carriers of at least on ApoE ε4 allele had three times higher increase in PiB binding than non-carriers. Even though there was a significant inverse correlation between episodic memory and PiB binding at baseline in MCI subjects and normal controls, no close relation was seen between cognitive decline and increase in PiB retention.

In the second year of ADNI, a project was started up using PIB as PET tracer, because of its increasing importance as a biomarker (20). Jagust et al describes some early results after one year follow-up. Of the 103 subjects enrolled at 14 different sites, follow-up data existed for 80 subjects, including 17 normal controls, 50 diagnosed with MCI and 13 with AD. The PIB-PET images were analyzed by an automated ROI method. SUVR was measured relative to cerebellar gray matter. An average was made of SUVRs of the four regions anterior cingulate cortex, frontal cortex, parietal cortex and precuneus, and this value was used in comparisons between subjects and to track longitudinal change. A subject was defined as PIB positive if average SUVR exceeded 1.50. At baseline, 47 % of the normal controls, 72 % of the MCI subjects and 89 % in the AD group were PIB positive. There were only small and insignificant changes in group average SUVR values after one year for all the three groups, but on individual basis 22 % of the PIB positives showed a significant change in PIB uptake, and 8 % of the PIB negatives. The report does not say if any of the MCI subjects converted to AD during this year, and if so, what the PIB status at baseline and longitudinal change was.

In another report, PIB PET images and MRI data from ADNI and another longitudinal study, the Mayo Clinic Study of Aging, were analyzed as one sample, by Jack et al (43). This made a total of 61 subjects, including 21 normal controls, 32 aMCI subjects and 8 AD subjects. They underwent clinical evaluation and PET and MRI scans twice, approximately one year apart. Diagnostic categories of the

subjects were set at consensus conferences, and 28 % of the MCI subjects progressed to an AD diagnosis. One of the cognitively normal subjects progressed to MCI status. An automated ROI method was used to analyze the PET images, and PIB ratio values were calculated by dividing median PIB uptake in a ROI with median uptake in cerebellar grey matter. PIB ratio values from the prefrontal, orbito-frontal, parietal, temporal, anterior cingulate and posterior cingulate cortices/precuneus were combined to a global cortical ratio. A global cortical ratio exceeding 1.50 defined the subject as PIB positive. The two MRI scans of each subject were used to calculate ventricular expansion rate as a measure of brain atrophy. At baseline, 29 % of the normal subjects were PIB positive, 59 % of the MCI subjects were the same, and all but one of the AD subjects were PIB positive. Also in this study the average annual change in global cortical PIB ratio was small for all the three groups, and no significant difference between the groups were shown. The change was greater for the PIB positives than PIB negatives among the MCI subjects, but there was no such difference among the normal controls. The ventricular expansion rate was significantly different between the groups, and was greatest for the AD group and smallest for the group of normal controls. This implies an acceleration in atrophy rate as Alzheimer's disease progresses. The ventricular expansion rate also correlated with the change in CDR-SB and MMSE, which was not the case for annual PIB PET change. There was no significant correlation between ventricular expansion rate and change in PIB uptake values. It is not reported whether the 8 MCI converters were PIB positive at baseline.

Comparable results were found in another recent study (44). Koivunen et al studied twenty-nine MCI subjects and 13 controls with PIB PET, MRI and neuropsychometry at baseline, and it was repeated after 2 years in the MCI subjects. At follow-up, 17 (59 %) had converted to AD. Among the converters, 87 % were carriers of the ApoE ε4 allele, as compared to 25 % of the non-converters. The PET images were analyzed with both ROI method and VBA. The 10 predefined regions included anterior and posterior cingulate, lateral frontal, lateral temporal and parietal cortices, caudate nucleus, putamen, thalamus and pons. In general, PIB uptake values were higher at baseline in the MCI converters than in the non-converters, especially in the posterior cingulate cortex. However, only in the non-converters a significant increase in PIB uptake over the two-year period was found; in anterior and posterior cingulate cortices, temporal and parietal cortices and putamen. The PIB images were not classified as being PIB positive or negative, but high region-to-cerebellum ratios (more than 1.5) was more frequent at baseline in the MCI converters in certain regions. The posterior cingulate cortex region-to-cerebellum ratio was high in 94 % of the MCI converters, and the results of using this in predicting conversion to AD is given in table 4. Hippocampal atrophy was visually graded from 0 to 4 by an experience neuroradiologist blinded to the clinical results. Atrophy was present in both converters and non-converters at baseline, and it increased over the follow-up period. A suggested interpretation of these results is that PIB uptake increases early and changes relatively little as the disease progresses, whereas hippocampal hypertrophy is more related to disease severity. Also in this study the follow-up period is relatively short, and it is uncertain whether some of the non-converters, and more specifically those with high regional PIB uptakes, later will be diagnosed with AD.

In another study by Okello et al, which was partly the same research group as Koivunen et al, the subjects were defined as being PIB positive if the PIB binding ratio compared to cerebellum was more than 2 standard deviations greater than the control mean in all six predefined ROIs (45). This

criterion was fulfilled by 55 %. The resulting ability of predicting conversion to AD is summarized in table 4. The converters showed higher PIB retention in all cortical brain regions. Those who converted to AD within 1 year had higher PIB retention values in anterior cingulate and frontal cortices compared to slow-converters and non-converters.

Three different clinical subtypes of MCI have been studied longitudinally by Wolk et al (46). A group consisting of subjects categorized as either single domain amnestic MCI (sd-aMCI), multi-domain amnestic MCI (md-aMCI) or non-amnestic MCI (non-aMCI) was followed up to 3 years. The overall results from this study are given in table 4, seeing the whole sample as a group of MCI subjects. Subjects were classified as PIB positive if the regional uptake ratio was more than the 75 percentile of the values from a control group in one or more of seven selected ROIs. More than half of the subjects in each MCI subtype group were PIB positive, also the non-amnestic MCI subjects. Nearly all multi-domain amnestic MCI subjects were PIB positive (5/6). Verbal delayed recall was significantly worse among the PIB positives. It was not a significant difference in grey matter loss in the medial temporal lobes (including the hippocampi) in PIB positive amnestic MCI subjects compared to negative subjects, but comparing with controls there was. Only subjects in the amnestic subgroups and only PIB positive subjects converted to AD during the follow-up period.

In the first longitudinally study using PIB PET imaging , by Forsberg et al, both PIB and FDG PET scans were obtained from 21 MCI subjects (47). Also CSF samples were taken at baseline. The subjects were followed, and 33 % converted to AD during that period. ROI based analysis was used to quantify PIB and FDG uptake in frontal, parietal and temporal cortices, posterior cingulum and subcortical white matter. Eleven patients showed high PIB retention in the frontal, parietal and temporal cortices, defined as more than one standard deviation above the mean level in a control group. All the converters were amnestic MCI subjects, and they all had high PIB values. The converters differed as a group significantly from the non-converters with respect to higher PIB retention in the posterior cingulum, a higher percentage of the ApoE $\varepsilon 4$ allele carriers (85 %), lower CSF Aβ42, lower MMSE test score and reduced episodic memory. Significant correlations were observed between CSF Aβ42 and PIB retention in the frontal cortex and posterior cingulum. Also, PIB uptake in frontal and temporal cortices and posterior cingulum correlated negatively with episodic memory. There was no correlation between glucose metabolism and PIB retention in any of the brain regions, and FDG uptake did not differ significantly between converters and non-converters.

One way of comparing these studies is to look at the capability of PiB PET as a diagnostic test for AD in MCI subjects. Values for sensitivity, specificity and positive and negative predictive values are derived from text, tables and figures presented in the articles, and they are listed in table 4.

Table 4. *Summarized results of PIB PET studies of MCI subjects with respect to AD conversion.*

Study (Ref)	**N**	**Age ± SD**	**M/F**	**Entry diag-nosis; Mean MMSE**	**Average follow-up time (months)**	**Con-vert-ers; Ann-ual rate (%)**	**Sens./spec.; PPV/NPV; Accuracy (%)**	**Data analysis**	**Image scaling**	**Discri-minating brain area**
Villemag ne et.al. 2011 (42)	65	73 ± 9	36/29	MCI; 27	20	48; 29	97/56; 67/95; 75	Both semi-automated and fully automated ROI method	Cere-bellum	Frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions
Okello et.al. 2009 (45)	31	69 ± 7	19/12	aMCI; 28	32	48; 18	93/81; 82/93; 87	Analyze and SPM99/six predefined ROIs and VBA	Cere-bellum	Anterior cingulate,poste rior cingulate, frontal, temporal, parietal and occipital cortices
Koi-vunen et.al. 2011 (44)	29	71 ± 6	18/11	MCI; 27	24	59; 30	94/58; 76/88; 79	Imadeus and SPM2/10 predefined ROIs and VBA	Cere-bellum	Posterior cingulate cortex
Wolk et.al. 2009 (46)	23	70 ± 9 (of 26 sub-jects at base-line)	19/7 (of 26 sub-jects at base-line)	12 sd-aMCI, 6 md-aMCI, 5 non-aMCI; 27	21	22; 13	100/56; 38/100; 83	11 predefined ROIs/SPM5	Cere-bellum	Frontal, anterior cingulate, precuneus, parietal, lateral temporal and lateral occipital cortices and occipital pole
Forsberg et.al. 2008 (47)	21	63 ± 8	8/13	12 a-MCI, 9 non-aMCI; 28	Not reported	33; N/A	100/71; 64/100; 65	5 predefined ROIs	Cere-bellum	Posterior cingulate cortex

The accuracy ranges from 65 – 87 %, the sensitivity from 93 – 100 % and specificity from 56 – 81 %. As discussed earlier, the positive predictive value is of limited interest because it is proportional to the prevalence of AD in the cohorts, which is higher in these studies than in the community

population. But as a parameter for comparison of similar studies, it has some value. Mean age and mean MMSE score at baseline and annual conversion rate could say something about sample similarity. One could expect that higher mean age, lower mean baseline MMSE and high annual conversion rate implied more affected MCI subjects and thus easier to diagnose as early AD. Villemagne et al studied a sample of older subjects, with mean MMSE in the lower range, and also the converters and non-converters differed by 2 points on MMSE, and the annual conversion range was in upper range, of 29 %.But they got the poorest result in terms of accuracy. The sensitivity was very good, however, of 97 %. This is the most trustworthy result, due to the largest sample. Koivunen et al studied a smaller, but quite similar sample in terms of age, MMSE and conversion rate, and they got very much the same results.

In general the sensitivities are high, but the specificities are quite low. In most cases the cut-off value categorizing the subjects as PiB positive or negative would have an impact on the sensitivity versus specificity, and they differed in the studies in table 4. Both Villemagne et al and Koivunen et al uses a regional-to-cerebellum cut-off value of 1.5, as well as Jagust et al and Jack et al. Cortical PiB ratio values above the 75 percentile were categorized as PiB positive by Wolk et al. Forsberg et al did not define any cut-off criteria, but only PiB binding in posterior cingulate cortex was significantly different between the converters and non-converters, and all the converters had PiB uptake greater than the mean value of 1.7 in this ROI. Okello et al compared each ROI uptake ratio in an MCI subjects with the mean value plus two standard deviations of the same ROI in the control subjects. If it was higher in all the six predefined ROIs, the MCI subject was classified as PiB positive. Okello et al got reasonably good specificity as well as sensitivity, and thus the highest accuracy, but to what extent this is due to the different approach in defining PiB positivity is difficult to determine.

In many of the studies, selected predefined ROIs are averaged to a global cortical value of uptake ratio, and this is used in the analysis of PiB PET imaging. Other studies focus more on what ROIs are most affected in the MCI subjects. Both Okello et al and Koivunen et al found that the baseline PiB retention was most increased in the posterior cingulate cortex in the converters compared to controls. The latter study also observed a greater uptake in anterior cingulate and frontal cortices in those subjects that converted within a year. Comparing converters and non-converters, Forsberg et al saw that the posterior cingulate cortex was the only ROI with significant difference.

In four of the described studies, the subjects underwent PiB PET scans also at follow-up. Jagust et al reported that no significant increase in PiB binding was seen at follow-up measurements one year later on a group level. Koivunen et al found that there was a significant increase after two years in the non-converters in several cortical brain regions, including anterior and posterior cingulate cortices, parietal and temporal cortices and putamen, but no significant difference was seen in the MCI subjects converting to AD. Both Jack et al and Villemagne et al found small but significant increase in PiB retention. The former did not see any difference between cognitively normal, MCI or AD groups, but there was a greater annual change in PiB positive MCI subjects compared to those who were negative. Villemagne et al found that the difference was significant for the MCI and AD patients, and also for PiB positive cognitively normal subjects. Neither of the two studies found any significant difference in increase for specific regions of interest.

Villemagne observed that PiB change significantly correlated with MMSE decline seeing the whole sample as one, but not with change in episodic memory. Jack et al did not find any correlation between the PiB change and change of CDR-SB, but a possible relation with MMSE change was seen. PiB positive subjects achieved significantly worse score on verbal delayed recall test at baseline than PiB negative subjects in the study of Wolk et al (46). Forsberg et al found PiB binding in frontal, temporal and posterior cingulate cortices to correlate negatively with episodic memory performance (47).

MRI-measurements of grey matter volume was done in three studies and compared with PiB PET as a biomarker. Jack et al and Koivunen et al could evaluate the change in volume over time because of repeated MRI scans at follow-ups, while Wolk et al only had clinical assessment at follow-up. Jack et al found that the rate of ventricular change was greatest for the AD group and least for the cognitively healthy group. In the MCI subjects, it was more pronounced in the PiB positive subjects. The rate of ventricular change was clearly inversely correlated with cognitive decline, as measured by CDS-SB and MMSE. Koivunen et al observed that baseline hippocampal atrophy was higher on the left side in the converters and on the right side in the non-converters compared to controls. After two years there was a significant increased hypertrophy on both sides in all MCI subjects. Wolk et al saw that the PiB positive amnestic MCI subjects had significant hippocampal atrophy compared to controls, while the PiB negative subjects did not. There were not reported any attempts of using the MRI measurements to predict subsequent conversion to AD in any of these studies.

It was a significantly higher PiB uptake in ApoE ε4 carriers than in non-carriers in the cohort of Villemagne et al, particularly in the healthy subjects and the MCI patients. The PiB increase after 20 months was 3 times larger in the carriers compared to the non-carriers. Of the MCI subjects converting to AD, 90 % were carriers of the gene, compared to 38 % of the non-converters and 31 % of the normal controls. In the study of Koivunen et al, 82 % of the converters and 25 % of the non-converters were carriers, while Forsberg et al found the numbers to be 85 % of the converters and 57 % of the non-converters.

Only Forsberg et al included CSF sampling in their study, and it was seen a significant correlation between CSF $A\beta_{1-42}$ levels and PiB retention in the frontal and posterior cingulate cortices. This was also the only study performing both FDG PET as well as PiB PET scans, but they found no correlation between glucose metabolism and PiB binding.

None of the studies combined PiB binding values and other biomarker parameters in order to enhance the diagnostic accuracy of AD in the MCI patients.

3.3 PET with ^{18}F-Florbetapir

The next activities of the PET core in ADNI will include the use of ^{18}F-labeled florbetapir, also called ^{18}F-AV45, in amyloid imaging (20). At the same time point the subjects will also be studied with FDG-PET, MRI and CSF and blood biomarkers.

Results from a longitudinal study of PET imaging with florbetapir with neuropathologic assessment after death were recently published by Clark et al (48). The subjects were terminal ill patients who were willing to undergo PET scan and donate their brains for research after death. Of the 35 subjects studied, 9 were cognitively normal, 3 had MCI, 17 were clinically diagnosed with AD and 6 with other

dementia disorders. The florbetapir PET images were visually rated from 0 (no amyloid) to 4 (high levels of cortical amyloid) by 3 nuclear medicine physicians, which were blinded to other information about the patients. The median rating served as outcome variable. Also a quantitative analysis was done, calculating cortical to cerebellar uptake ratio (SUVR) in 6 predefined regions of interest (frontal, temporal, parietal, anterior cingulate, posterior cingulate cortices and precuneus) plus cerebellum as reference region. From the same 7 regions, tissue blocks from both hemispheres were dissected and analyzed with respect to β amyloid aggregation and neuritic plaque density. In addition, a neuropathologic diagnosis was made using standardized criteria (CERAD and NIA-Reagan). It was found a good correlation between the SUVR value and postmortem measurement of amyloid for each region. The blinded visual reading of AD positive PET images (rating 2 – 4) and the neuropathologic diagnosis of AD (CERAD "definite" or "probable") was in agreement in 18 of 19 cases, whereas 16 of them were clinically diagnosed correctly with AD. All 16 subjects that was neuropathologically diagnosed non-AD (CERAD "no" or "possible") was rated florbetapir PET negative (rating 0-1) visually, but one of these had received a clinical diagnosis of AD. None of the 3 MCI subjects were positive on the PET scan or diagnosed with AD by the neuropathologic examination. Thus the overall accuracy of florbetapir was 97 % in diagnosing AD correctly. When all the 152 individuals enrolled in the project are finally examined neuropathologically, the accuracy will be provided with stronger confidence. Eight of the 20 authors had affiliations with the commercial manufacturer of florbetapir. The report was later commented on, regarding inter-rater variability in assessment of the PET scans (49). This information was not provided in the article, but was submitted to the US Food and Drug Administration (FDA) in a report for approval of florbetapir from the commercial manufacturer. It appears that the three raters only agreed on the same score in 17 % of the cases, and that in one fourth of the cases the disagreement would give different conclusions with respect to subjects being amyloid positive (score 2 – 4) or negative (score 0 – 1) (50). However, one can see from the published article that if the mean neocortical SUVR values are used with a cut-off value of 1.17 to categorize the subjects as florbetapir PET positive or negative, they are 100 % in accordance with the CERAD diagnoses (48).

Longitudinal studies including MCI subjects are ongoing, but are yet not reported, other than briefly in a conference abstract (51).

Fleisher et al pooled data from 4 registered phase I and II trials of florbetapir (52). That gave a total of 210 subjects, including 82 cognitively normal volunteers, 60 MCI subjects and 68 patients with probable AD. A ROI analysis was performed on the florbetapir images, and mean regional-to-cerebellar uptake ratios (SUVRs) were calculated for 6 predefined regions: medial orbital frontal, temporal, anterior and posterior cingulate, parietal lobe and precuneus. A global cortical mean SUVR was obtained by averaging these 6 SUVRs. The three different groups differed significantly with respect to the cortical mean SUVRs. In the healthy controls, the florbetapir binding increased linearly with age. In the AD and MCI groups, greatest uptake was seen in precuneus, the posterior cingulate, the parietal lobe and the temporal and frontal cortices.

They derived a cut-off value defining florbetapir PET positive from the cohort of 19 neuropathologically verified AD subjects described above (48). All of them had a cortical mean SUVR of 1.17 of more. Hence, the cut-off value for amyloid positive was set to this value. They also defined an amyloid negative cut-off value, based on a cohort of 46 young (age 18 – 40 years) that were all

ApoE ε4 non-carriers and therefore were very unlikely to have cortical amyloidosis. So the amyloid negative cut-off value was set to 1.08, which was the maximum cortical mean SUVR in this group. Thus 81 % of AD patients were florbetapir PET positive, 40 % of the MCI subjects and 21 % of the healthy controls. And 85 %, 47 % and 28 % of these groups, respectively, were above the florbetapir negative cut-off value. The hypothesis is that using the negative cut-off value, those individuals in the earliest stages of amyloid accumulation can be identified. Only longitudinal studies can answer that.

3.4 PET with ^{18}F-Florbetaben

One other promising amyloid tracer is ^{18}F-Florbetaben, also known as ^{18}F-BAY-94-9172 or AV-1. Recently, Villemagne et al published results from a multicenter study involving 109 subjects, including 30 patients with AD, 20 MCI subjects, 32 controls, 11 patients with FTLD, 7 with DLB, 5 with Parkinson disease and 4 with vascular dementia (53). Neocortical florbetaben binding was expressed as the average SUVR of the area-weighted mean of the frontal, superior parietal, lateral temporal, lateral occipital and anterior and posterior cingulate ROIs. A cut-off value of 1.4 for cortical SUVR was calculated by hierarchical cluster analyses, to define the subjects as amyloid positive or negative. Also visual rating of the PET images by to nuclear medicine physicians was done. All AD patients except one were amyloid positive and showed greater florbetaben retention in the frontal and posterior cingulate cortex/precuneus and slightly less in the lateral temporal and parietal cortex. Also 60 % of the MCI subjects and 16 % of the controls had elevated florbetapir uptake. In the MCI group, the posterior cingulate, parietal, temporal and frontal cortices and the striatum showed significantly higher levels compared to the control group.

Comparable results were found by Barthel et al in a phase II diagnostic study involving 81 AD patients and 69 healthy controls (54). Of the AD patients, 81 % showed elevated levels of florbetaben, and 10 % of the healthy controls did the same. In the AD patients all neocortical regions showed significantly higher uptake compared to the controls, and the posterior cingulate cortex was found to be the best discriminator.

There have not been any published studies of the correlation of florbetaben PET imaging results and post-mortem neuropathological findings yet. An ongoing phase 3 trial will provide such results (55). So far no other longitudinal studies of florbetaben have been published either, only some preliminary results have been published in an abstract (56).

3.5 PET with ^{18}F-Flutemetamol

Flutemetamol, also called ^{18}F-GE-067 is the fluorine-derivative of PiB, and is expected to show the same qualities in imaging of amyloid β.

In a study of 27 patients with AD, 20 amnestic MCI subjects and 15 elderly and 15 younger healthy controls, it was shown that flutemetamol PET images can discriminate patients with AD from normal controls with high sensitivity and specificity (57). The cut-off value defining uptake values as abnormal was calculated to be 1.56 based on values of the elderly healthy controls and the AD patients. It resulted in 93 %, 50 % and less than 1% of the AD patients, MCI subjects and elderly healthy controls being flutemetamol PET positive, respectively. The most significant differences in uptake value ratios between AD patients and elderly healthy controls were in the lateral frontal, lateral temporal, lateral parietal and posterior cingulate cortices and striatum. The uptakes of

flutemetamol and PiB in the same subjects were highly correlated in the same volumes of interest. In almost all regions, the linear regression slope was almost equal to 1, except in subcortical white matter and pons. This means that flutemetamol uptake is higher than that of PiB in white matter, as it is for all the ^{18}F-labelled stillbenes.

No truly longitudinal study with flutemetamol PET scans has been done, but images were taken of 7 patients with normal pressure hydrocephalus that previously had undergone biopsy from the right frontal cortex (58). In all of the four subjects with abnormal images there was also found amyloid plaque pathology in the biopsy tissue. The three normal scans were in patients with no evidence of Aβ pathology. Also there were found significant correlation between the estimated amount of amyloid β deposition in the biopsy samples and the flutemetamol uptake value ratio of the corresponding ROI in the PET images.

3.6 PET with ^{18}F-FDDNP

FDDNP was the first amyloid imaging tracer reported, and has been shown to bind to both the extracellular β amyloid plaques and the intracellular neurofibrillary tangles (59). Results from a study of 25 patients with AD, 28 MCI subjects and 30 normal controls, showed that global FDDNP uptake discriminated the patient groups with better accuracy than FDG glucose metabolism and MRI estimated medial temporal volumes (60). The different groups had significantly different uptake values. Twelve subjects were followed longitudinally with a clinical assessment after 2 years. The 9 subjects that were clinically stable had only small increases in global FDDNP binding. One healthy subject was reclassified to have MCI, and two MCI subjects had developed AD. In these three subjects there were seen greater increases in FDDNP uptake. One patient with AD died 14 months after baseline, and a neuropathological examination was performed. It showed good correspondence between regions with high concentrations of plaques and tangles and the regions with high FDDNP uptake on PET images.

Another study, however, did not find significant differences between AD, MCI and normal controls on group level, only between the AD group and the normal controls (61). The subjects underwent both PiB and FDDNP PET scans, and the global binding of PiB was nine-fold higher than of FDDNP. In the AD patients, the PiB uptake was increased in all the cortical regions, but with the smallest increase in the medial temporal lobe. This was the region with the highest uptake of FDDNP for all groups .This is possibly explained by the different distribution of senile plaques and neurofibrillary tangles in the brain.

No larger longitudinal studies of FDDNP PET imaging have been reported.

4 Discussion

4.1 Summarizing and comparing PET studies

The longitudinal studies previously described of FDG PET that followed the subjects until death and post-mortem neuropathologic assessments showed good agreement between the FDG uptake and autopsy findings. FDG PET is found to diagnose AD with a sensitivity ranging from 84 – 98 % and specificity from 67 – 80 %, which means that a large number of AD patients would be correctly

diagnosed by FDG PET scanning, but also there would be a considerable amount of subjects of false positives, because the method is not so specific.

Mosconi et al saw that subjects could show glucose hypometabolism several years before the onset of symptoms, and Jagust et al experienced that FDG PET gave the same test results as clinical evaluation 4 years later (15;18), which indicates a capability of FDG PET to detect preclinical and early AD. FDG PET images of the AD subjects reveal glucose hypometabolism in the posterior cingulate cortex and temporoparietal areas. Also areas in the frontal cortex may be affected. Fisher et al observed asymmetry in half of the subjects, and most often the right hemisphere was hypometabolic (14). In the preclinical stage, hippocampal hypometabolism is an early finding in the small study of Mosconi et al (18).

The other selection of FDG PET studies evaluated in this review is of MCI subjects, in whom FDG PET is used to diagnose early AD, and clinical evaluation of the disease stage (MCI or AD) at follow-up is the gold standard. Accuracies for the different studies range from 56 – 90 %, sensitivities from 57 – 93 % and specificities from 47 – 91 %. The two largest studies are analyses of the ADNI data, with 85 and 94 MCI subjects, and probably with substantial sample overlaps (21;24). The results achieved by Landau et al and Herholz et al are in the lower range and are surprisingly poor, compared to the earlier and smaller studies. Leaving these results out, the accuracies, sensitivities and specificities would range from 85 – 90 %, 82 – 93 % and 82 – 91 %, which are fairly good results. One would expect the largest studies to be the most trustworthy, but the fact that ApoE ε4 gene carrier status was the most accurate predictor makes one question the analytical approach. If this finding is correct, it would be unexpected based on earlier studies. Researchers can apply for access to the ADNI database to analyze the different biomarker measurements, and hopefully more studies on this material will be published. Herholz et al achieved a better accuracy than Landau et al, 64 % versus 56 %, and Walhovd et al and Landau et al concluded contrarily about whether CSF proteins significantly correlate with cognitive decline or not, indicating that differences in analytical methods have significant impact on the results (21;23;24).

Both Landau et al and Herholz et al found a close correlation between the longitudinal decrease in glucose metabolism and cognitive decline (22;24). Also the variation was less compared to change in ADAS-Cog scores, and thus FDG PET is a better parameter for measuring cognitive decline in clinical trials. The greatest reduction in glucose metabolism was seen in the medial temporal lobe and posterior cingulate cortex in the MCI subjects.

In the MCI subjects converting to AD during the follow-up period, there is found hypometabolism in the posterior cingulate cortex, temporoparietal areas, and sometimes also in lateral frontal and orbitofrontal cortex at baseline measurements. This is in accordance with the findings from the other FDG PET studies, of AD subjects eventually neuropathological examined. Reduced hippocampal metabolism was found to predict future development of AD in cognitively healthy subjects, and hippocampal hypometabolism was seen in MCI subjects that did not convert to AD but were declining cognitively (25;29). This further supports the hypothesis of hippocampal hypometabolism as an early predictor of later AD development.

Reviewing the longitudinal studies of PiB PET leaves several questions about the ability to measure AD pathology in the form of fibrillar amyloid plaques. Unfortunately there are few studies of PiB PET

imaging and later post-mortem neuropathologic assessment of AD patients, only case studies are described. In some of these the findings are consistent, for instance high PiB uptake and moderate level of neuritic plaques, good correspondence between ROIs showing increased binding and brain areas with amyloid β, or subjects with negative PiB PET scan and sparse findings at autopsy (38;40). But there are also cases of inconsistent findings of PiB binding and neuropathology, and there is a need of studies of larger samples with AD patients, in order to fully understand what PiB PET is measuring. Probably PiB binds to fibrillar amyloid β, but it is uncertain to what extent other forms of amyloid β is imaged on PiB PET scans. For instance, it is discussed that PiB may bind to vascular amyloid plaques, which is present in cerebral amyloid angiopathy and often, but not always associated with AD (38;41). Also, to what extend PiB binds to polymorphic or diffuse plaques is discussed, as attempts of explaining false positive of false negative PiB PET scans (38;39).

This uncertainty has consequences for the interpretation of PiB positivity in cognitively normal subjects and stable MCI subjects. Will these subjects eventually develop AD, or does PiB also bind to amyloid β not necessarily contributing to AD pathology? The longitudinal studies of PiB PET with clinical evaluation as gold standard do not answer this either, due to short follow-up periods of 1 – 2 years.

The prediction accuracy of PiB PET in diagnosing early AD in the MCI subjects ranges from 65 – 87 %, the sensitivity from 93 – 100 %, and specificity from 56 – 81 %. Generally, this sensitivity for PiB is good, and most of the patients that develop AD can be diagnosed at the MCI stage of the disease. The specificity is rather poor, but must be interpreted with caution. At this point of PiB PET research there is uncertainty about whether false positive subjects eventually will be diagnosed with AD also clinically, develop other dementia diseases or will remain stable. Longer follow-up periods would answer this.

In several studies, the distribution of PiB binding is observed to be of bimodal distribution, either elevated or not, and most evident in the groups of cognitively normal and MCI subjects (34;62). Of the studies in this review, Villemagne et al observed bimodal distribution in the normal controls, and derived the cut-off value for PiB positivity based on this (42). Also Wolk et al found a bimodal distribution in the MCI group, while Jack et al reported of a continuous distribution in PiB retention (43;46). There is yet no consensus of the cut off value defining positive versus negative PiB PET images, but there seems to be a trend in the latest and largest studies towards an uptake value of 1.5 scaled to the cerebellar PiB binding (20;42-44). This cut-off value could of course have an impact on the levels of sensitivity and specificity.

The posterior cingulate cortex seems to be the predefined ROI that in most studies show significant difference in PiB uptake when MCI converters are compared to normal controls or non-converting MCI-subjects (44;45;47). A significantly increase in PiB retention was seen in anterior cingulate and frontal cortices in the subjects that converted to AD within a year.

Serial PiB PET scans were taken in four of the studies reviewed. Both Jagust et al and Jack et al found only small and not significant changes in PiB retention after one year, while Villemagne et al saw a significant increase in the MCI and AD groups as well as in the PiB positive normal controls (20;42;43). The increase was not significantly different among the clinical groups, but was significantly greater among PiB positive MCI subjects in Jack et al and among both PiB positive MCI

subjects and normal controls in Villemagne et al, compared to PiB negative subjects. There were no significant differences in retention increase for any specific regions of interest (42;43). Koivunen et al found that there was a significant increase after two years in the non-converters in several cortical brain regions, but no significant difference was seen in the MCI subjects converting to AD (44).

There has been a hypothesis that PiB retention reaches a plateau early in the pathophysiologic development of AD, probably at a preclinical stage, and after that changes very little as the disease progresses (63). These studies are not contradictory to that hypothesis, but the results of Villemagne et al might indicate a small gradient in PiB retention change with time instead of an asymptotic curve, as pointed out in their article (42).

The PiB retention change during 20 months correlated significantly with MMSE decline for the total sample, found by Villemagne et al, and there were seen a possible relation after only one year of follow-up by Jack et al. There were no correlations with change in episodic memory of CDR-SB scores (42;43).

It was a significantly higher PiB uptake in ApoE ε4 carriers than in non-carriers, particularly in the healthy subjects and the MCI patients, and the PiB increase after 20 months was 3 times larger in the carriers compared to the non-carriers (42). Of the MCI subjects converting to AD, 82 – 90 % were carriers of the gene, compared to 25 – 57 % of the non-converters (42;44;47).

It is attempting to compare the results of prediction capability of FDG PET and PiB PET, as summarized in table 3 and 4, respectively. The samples seem to be in the same range with respect to baseline mean MMSE, but the subjects of the FDG PET studies are in a higher age range. The annual conversion rates are comparable. Two of the FDG PET studies stand out because of considerable lower prediction ability, in terms of accuracy, sensitivity and specificity (21;24). These are also the largest studies, analyzing the ADNI data, and if these two studies are representative of what is possible to achieve in large cohorts, FDG PET is less accurate, less sensitive and less specific than PiB PET in predicting later conversion to AD in MCI subjects. If these two studies are not representative however and are excluded, the comparison of FDG and PiB PET indicate that PiB PET is more sensitive while FDG PET is more specific and also more accurate, see table 5.

Table 5. *Range of accuracy, sensitivity, specificity, PPV and NPV from studies of the two PET methods, summarized from table 3 and 4.*

	FDG PET		PiB PET
	ADNI studies	Non-ADNI studies	
Accuracy	56 – 64	85 – 90	65 – 87
Sensitivity	57 – 75	82 – 93	93 – 100
Specificity	47 – 67	82 – 91	56 – 81
PPV	41 – 45	68 – 85	38 – 82
NPV	77 – 79	91 – 97	88 – 100

One cannot conclude based on this rough comparison, and optimally there should be longitudinally studies of both PET methods in the same subjects. Such data probably exists in the ADNI database, but no comparison analysis of FDG and PiB PET has been reported yet. Only one study of those reviewed here involved imaging with both FDG and PiB PET. Forsberg et al found no correlation between glucose metabolism and PiB binding (47). This is one of the smallest studies, of only 21 MCI subjects, and they did not find any significant difference in FDG uptake between converters and non-converters either, in contrast to the other longitudinal FDG PET studies of MCI subjects described in this review.

In both of the methods, there is no standardized method of setting the cut-off value defining abnormal versus normal images, and this is expected to have an impact on differences between studies in the diagnostic capability of early AD.

In these studies reviewed, the accuracy is never 100 %. The accuracy shows to what extent the PET imaging results are in accordance with the clinical diagnosis at follow up evaluation, usually 1-3 years after the PET scan. When clinical evaluations are used as gold standard, it is hard to establish what part of the discrepancy from 100 % merely mirrors the uncertainty in the clinical diagnosis and what part is the uncertainty in the method itself. There is a hypothesis of cognitive reserve, which is meant to explain the differences in the degree of cognitive impairment for subjects with the same degree of AD pathology in the brain. For instance it is found that people with higher degree of education have more advanced AD pathology than those with less education at the same level of symptoms. This might be explained by a higher number of neurons and higher synaptic density (7). Cognitive reserve may also explain that younger MCI subjects show more extensive hypometabolism but obtain higher scores on neuropsychological tests than older subjects at the same stage of disease as measured by MMSE (31). Genetic vulnerability, life style factors and co-morbid conditions influence on the threshold for cognitive impairment caused by amyloid β aggregation. Clinical symptoms will reflect the degree of neuronal damage differently, and thus the clinical evaluation might not reflect the actual pathology. Cognitive reserve is not a factor in biomarker measurements.

Also a comparison of the regional differences in tracer uptake between FDG and PiB in the same MCI subjects would provide interesting information. The posterior cingulate cortex seems to be most often affected in the MCI converters, in terms of both glucose metabolism and amyloid deposition. In the FDG PET studies also parietotemporal areas are often mentioned, while anterior cingulate cortex and frontal areas might seem more important in the PiB PET studies. The effect of atrophy will influence differently on FDG and PiB PET measurements, in the sense that glucose hypometablism will be more severe while PiB retention will be less pronounced. Partial volume corrections are sometimes performed in FDG PET studies to eliminate volume as confounding factor on glucose metabolism.

In a study of 20 patients with mild AD, both longitudinal FDG and PiB PET imaging were performed 27 months apart (64). Voxel-based analysis was performed on the images, and they compared the regional overlaps of the two methods by Dice similarity coefficients. FDG PET showed hypometabolism in bilateral parieto-temporal and posterior cingulate cortices and precuneus and right dorsolateral prefrontal cortex. At follow-up hypometabolism increased, especially in the right temporo-parietal cortex. At baseline PiB retention was seen in bilateral parieto-temporal and

posterior cingulate cortices and precuneus, as well as orbitofrontal, medial and lateral prefrontal cortices. This pattern did not change much at follow-up measurements. The strongest intermodal similarity was actually between the baseline PiB PET and the follow-up FDG PET patterns, of 47 %. One possible interpretation of this is that the changes of hypometabolism follow the pattern of amyloid depositions with a temporal delay, and that amyloid depositions precede the neuronal damage. But again, longitudinal studies of MCI subjects involving both PET modalities are necessary to further investigate this.

There are also other tracers than PiB used in so-called amyloid imaging. The first amyloid tracer reported was the 18F-labeled tracer called FDDNP. This is thought to image neurofibrillary tangles as well as amyloid plaques. No larger longitudinal studies have been reported. The highest FDDNP binding is seen in the medial temporal lobe, which might be explained by a high density of neurofibrillary tangles in this region. It has been shown that global binding of PiB is nine-fold higher than of FDDNP in the same subjects (61).

There are three 18F-labelled tracers currently in clinical trials, which are expected to become commercially available, namely florbetapir (AV-45), florbetaben (BAY-94-9172) and flutemetamol (GE-067). These are also thought to image amyloid plaques, and their physical half-life of 110 minutes provides a practical advantage compared to 11C-PiB, with half-life of only 20 minutes. The 18-F labeled tracers may thus be produced centrally and distributed to the PET centers, while PiB requires an on-site cyclotron for local production.

Florbetapir will be included in the next phase of the ADNI project. One study including post-mortem neuropathologic assessment showed strong relation between the PET images and the autopsy findings (48). In MCI subjects and AD patients, the PET images show increased uptake of the 18F-labelled tracers in precuneus, the posterior cingulate cortex, the parieto-temporal lobes and frontal cortex. The uptake is higher than that of PiB in white matter (52;53;57). No longitudinal studies involving MCI subjects are published yet, but are expected to come within the next years.

4.2 Comparing with MRI methods

Structural MRI imaging is used to measure volume or atrophy, cortical thickness or density of tissue compartments, for instance gray matter. Especially grey matter volume loss is often assessed. In AD, the medial temporal lobe is affected most, and the hippocampus can be reduced with 20 % already at a mild stage (34). The lateral temporal, parietal and prefrontal lobes also show volume losses, but to a lesser extent and more variably across studies. It has been shown that hippocampal hypertrophy and posterior cingulate gyrus atrophy is associated with increased PiB retention, also in cognitively normal subjects. Also cognitively normal carriers of the ApoE ε4 allele experience greater hippocampus volume loss than non-carriers.

Of the FDG PET studies reviewed here, only two studies included MRI measurements (21;23). As seen from table 2, MRI was slightly less sensitive, a little more specific and just as accurate as FDG PET in predicting future conversion to AD in MCI subjects in the study of Landau et al. Walhovd et al found in their study that retrosplenial glucose metabolism measured showed the strongest correlation with cognitive decline, but also MRI measurements of retrosplenial thickness and hippocampal volume in MCI subjects showed significant correlations (23).

MRI-measurements of grey matter volume were done in three of the PiB PET studies. Serial MRI scans in the study of Jack et al showed that the ventricular change after one year was greatest for the AD group and least for the cognitively healthy group (43). In the MCI subjects, it was more pronounced in the PiB positive subjects. The rate of ventricular change was clearly inversely correlated with cognitive decline, as measured by CDR-SB and MMSE. Hippocampal atrophy was significantly increased after two years in all MCI subjects, in the study of Koivunen et al (44). Wolk et al saw that the PiB positive amnestic MCI subjects had significant hippocampal atrophy compared to controls, while the PiB negative subjects did not (46). MRI measurements were not used to predict subsequent conversion to AD in any of these studies.

In a recent study of longitudinal MRI data from ADNI by Misra et al, spatial patterns of brain atrophy and changes with time are analyzed by high-dimensional pattern classification (65). The sample included 103 MCI patients, of which 27 converted to AD within the follow-up period of 15 months. The aim was to determine predictors of short-term conversion from MCI to AD. There were found significant differences at baseline between AD converters and non-converters, even though the average baseline MMSE score was about the same, of 26 – 27, in both groups. The converters had reduced grey matter volumes in a number of brain regions, including the anterior hippocampus, amygdala, much of the temporal lobe and the insular cortex, posterior cingulate and orbitofrontal cortex. Also white matter reductions were seen, primarily in the periventricular frontal region, indicating increased periventricular small-vessel pathology in the converters. The last tissue type analyzed was cerebrospinal fluid, which was larger in the temporal horns of the lateral ventricles bilaterally. There were no significant differences in the rate of change of grey matter between the two MCI groups. A pattern classification method enabled a score, which defined the MRI images as either positive for AD pathology or not. The best classification accuracy in terms of identifying converters and non-converters based on baseline MRI data was 82 %. Also several non-converters had a score value indicating AD pathology, and could be expected to develop clinical AD in the future. The authors suggest that vascular pathology ought to be studied in tandem with brain atrophy, and could be important in the issue of predicting which subjects will convert to AD.

Also Ewers et al studied the ability of MRI measurements to predict conversion from MCI to AD based on longitudinal ADNI data. They used hippocampal volume and entorhinal cortex alone or in combination with CSF protein levels and neuropsychological tests (66). The sample consisted of 81 patients with AD, of the 130 MCI subjects and 101 healthy controls. Of the MCI subjects, 58 developed AD within the 3.3 years of clinical follow-up. Logistic regression analysis was used to discriminate the AD patients from the normal subjects, and then the model derived was applied to the MCI subjects, to predict AD conversion or not. In a second approach they tried the different combinations of biomarkers and neuropsychological tests to find the one that identified the converters and non-converters with the best accuracy, but limited to maximum 4 predictors. The best single-predictor was the right entorhinal cortex, with sensitivity of 53 %, specificity of 77 % and total accuracy of 69 %. Using four predictors, the best result was with the combination of right hippocampal volume, CSF p-tau181/Aβ, trail making test b (TMT-B) and age. This gave an accuracy of 76 %, sensitivity of 88 % and specificity of 68 %. This increase in accuracy was not significant however, and the authors raise the notion that the increased number of measurements may not be justified in terms of accuracy enhancement.

These two longitudinal ADNI studies of structural MRI both achieve better results than hippocampal volume in the ADNI study of Landau et al, as seen in table 2. The accuracies of 56 %, 76 % and 82 % differ quite a lot, taken into account that there must be some sample overlaps, and the different analytical methods must play a significant role. Comparing the studies of Ewers et al and Landau et al (table 2), entorhinal cortical thickness was a less sensitive, more specific and more accurate predictor of future AD than glucose hypometabolism and hippocampal volume. Also compared with the other ADNI FDG PET study of Herholz et al (in table 3), the entorhinal cortical thickness was less sensitive but more specific and accurate than FDG uptake, but compared with the other FDG PET studies the results of Ewers et al was poorer . The specificity of entorhinal cortical thickness seems to be in the same range as PiB PET, but is much less sensitive and thus less accurate than PiB PET, as seen in table 5.

Other MRI techniques like diffusion tensor imaging and functional MRI are expected to become more important in the early diagnostics of AD. MRI diffusion tensor imaging (DTI) is a technique that is used to measure microstructural changes in white matter fiber tracts. Fractional anisotropy (FA) is derived from the DTI data based on the movements of water molecules, and is a measure of fiber directionality and integrity. Mean diffusivity is the magnitude of the diffusion. In AD patients, the fibers connecting the hippocampus and posterior cingulate gyrus are impaired, and also fibers connecting the prefrontal cortex with the medial temporal lobe or the parietal cortex. Also cognitively healthy subjects with at least one ApoE $\varepsilon 4$ allele show reduced FA in the posterior cingulum, corpus callosum and other major white matter bundles (34).

In MCI subjects, it has recently been found that entorhinal white matter changes measured by DTI are significantly increased in amnestic MCI subjects compared to individuals with subjective memory complaints, but not fulfilling the MCI criteria, and that these changes were related to reduced story memory as measured by Wechsler Memory Scale – Revised (WMS-R) (67). Not many longitudinal studies of DTI measurements in MCI subjects has been published, but in a small study of 13 MCI subjects mean diffusivity in left hippocampus at baseline was significantly increased in the 6 subjects converting to AD within 19 months. Neither hippocampal FA nor volume differed significantly (68). In another small longitudinal study recently published, 14 amnestic MCI and 11 normal subjects were followed in 13 months (69). Only one of the MCI subjects converted to AD during this period. It was found no significant difference in baseline FA between the normal and the MCI subjects, and neither in FA decline.

In functional MRI (fMRI), blood flow and blood oxygen level is measured, which is believed to show changes in neuronal activity within a few seconds (34). It can be used to both image brain activity while specific tasks are performed or during resting state. The last years a brain network termed the default mode network (DMN) has received attention in fMRI studies of AD patients and MCI subjects. The DMN includes the medial frontal, temporal and parietal brain regions, and is most active during periods of rest and less active during engagement in cognitive tasks. In AD patients, fMRI show abnormal activity in the DMN compared to cognitively healthy subjects, with impaired activation during rest and less deactivation during memory tasks. In a longitudinal study of 31 MCI subjects, fMRI images were taken during memory tasks at baseline (70). They were followed clinically for 2.4 years, and 11 subjects converted to AD in this period. A quantitative DMN connectivity score was calculated, and this was significantly higher in the converters compared to the non-converters. It also

correlated with change in CDR-SB score. The DMN connectivity score did not significantly predict conversion when also baseline delayed verbal recall test results were taken into account.

4.3 Combining several imaging and non-imaging biomarkers

The last years there have been published studies using several imaging techniques and perhaps also neuropsychological tests, CSF sampling or ApoE ε4 genotyping within the same sample subjects. Especially the large multicenter studies like ADNI are providing such data. Usually the different modalities are analyzed individually and compared and correlated. Not so many studies combine the different methods to enhance the accuracy in determining diagnostic category (healthy controls, MCI subjects of AD patients) or predicting cognitive decline or conversion to AD in MCI subjects.

It was found by Walhovd et al that logistic regression analysis with the combination of measurement data from FDG PET, MRI morphometry and diffusion tensor imaging (DTI) could place 44 MCI subjects and 22 controls in the correct diagnostic category with 100 % accuracy (71). A longitudinal follow-up will determine to what extent this combination predicts conversion to AD in the MCI subjects.

Hinrichs et al used a fully multi-modal method incorporating all the different longitudinal measurements of AD pathology in ADNI (72). By using a method based on so-called Multi-Kernel Learning framework, they created a multi-modal disease marker to predict conversion from MCI to AD. The prediction capability is not given in numbers, but from one of the figures, this method seemed to identify very few of the converters, and definitely not providing better results than what is seen for FDG PET or MRI alone.

A kernel-based method was also used by Zhang et al to combine FDG PET, MRI and CSF measurements obtained from the ADNI database (73). The subjects included 51 AD patients, 99 MCI patients and 52 healthy controls. Within 18 months, 43 MCI subjects had converted to AD. Estimated grey matter volume and glucose metabolism are retrieved from 93 ROIs in both FDG PET and MRI images. They found that 91 % of the AD converters in the MCI group and 73 % of the non-converters were correctly classified, which is the sensitivity and specificity, respectively. The accuracy can be derived to be 81 %. These results are better than most of the other ADNI results presented here (21;24;66). Misra et al got a better accuracy though , of 82 %, in their MRI alone analysis (65).

A few of the studies reviewed here combined FDG PET imaging with another biomarker to enhance the prediction ability. Jagust et al experienced in their longitudinal study of AD patients including post-mortem neuropathologic assessment that the positive predictive value of the clinical AD diagnosis initially increased from 70 % to 84 % if also the FDG PET image was interpreted as positive for AD, which is most likely the clinical setting. The negative predictive value increased from 65 % if the diagnosis initially was not AD to 83 % if also the FDG PET image was negative (15).

Landau et al found that a combination of FDG PET and episodic memory, as measured by AVLT, predicted future AD conversion with the hazard ratio of nearly 12, compared to 2.7 and 4.3, respectively, for the two methods individually (21). Also Anchisi et al combined FDG PET and a verbal recall test to enhance prediction accuracy from 85 % to 94 %, and resulting in a sensitivity of 86 % and specificity of 97 % (26). Combining the FDG PET results and the ApoE ε4 genotype, Drzezga et al achieved 100 % sensitivity, defining those who were either FDG PET positive or ApoE ε4 carrier as test positive (28). The specificity was poor however, of 44 %. On the other hand, if test positivity was

defined to being both FDG PET positive and ApoE ε4 carrier, the specificity was 100 % and sensitivity 67 %.

These results of Drzezga et al are illustrated in the diagram in figure 1. All of those eight MCI subjects that were both FDG PET positive and ApoE ε4 carriers, seen in dark green in figure 1, developed AD. And none of those eight MCI subjects that were both FDG negative and ApoE ε4 non-carriers, as seen in white, developed AD. Of those five MCI subjects that were FDG PET positive but ApoE ε4 non-carriers, colored in light green, three developed AD. Also one of the nine subjects that were FDG PET negative but ApoE ε4 carriers, in the blue section, progressed to AD.

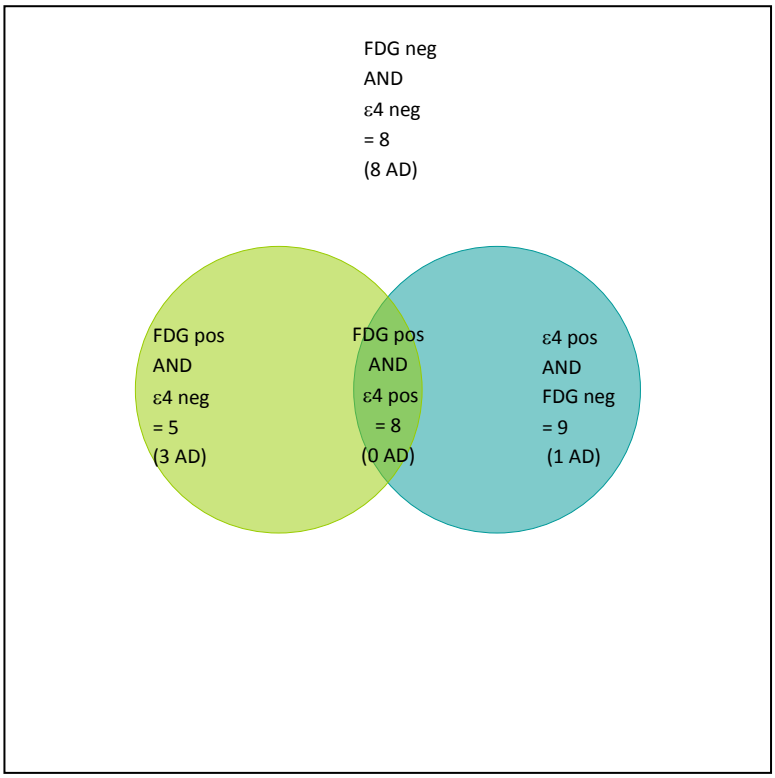

Figure 1. *Illustrating the results of combining FDG PET and ApoE ε4 status by Drzezga et al (28). The study comprised 30 MCI subjects, of whom 12 developed AD. In total, 13 subjects were FDG PET positive and 17 were ApoE ε4 carriers.*

Only 30 MCI subjects were studied by Drzezga et al (28), but it seems reasonable that future conversion to AD could be predicted with good accuracy for subjects being positive on both measures, and that being negative on both would be predictive for not progressing to AD. Based on the good results achieved by Anchisi et al (26), one could think that for the two remaining groups in which FDG PET and ApoE ε4 carrier status points in opposite directions with regards to AD conversion (FDG PET positive/ApoE ε4 non-carrier and FDG PET negative/ApoE ε4 carrier), verbal delay test scores could distinguish probable converters from non-converters. Anchisi et al found a cut-off value for the California Verbal Learning Test (CVLT) by ROC analysis, and Landau et al did the same for AVLT (21). It would have been interesting to apply this approach of combining FDG PET, ApoE ε4 carrier status and verbal delay test scores on a larger sample of MCI subjects, like the already existing data from the ADNI project.

5 Concluding remarks

The studies reviewed of FDG and PiB PET here show that conversion from MCI to AD can be predicted. What this means is that AD can be diagnosed by PET methods a few years before the clinical evaluation conclude with the same. In general, sensitivities are good and especially for PiB PET. The specificity is poorer, but longer follow-up time will reveal if some of the "false positives" in fact will become "true positives", because they decline cognitively at a slower rate. That would improve the specificity and accuracy.

A hypothetical model describing the time development of the five most validated biomarkers was recently published (63). Also the connections between the biomarkers and the different neuropathologic processes are sought explained. Biomarkers of amyloid depositions are CSF Aβ reductions and increased binding of PiB as measured by PET. This occurs in a pre-clinical stage of the disease, probably several years before onset of the first symptoms. When MCI is a fact, these biomarkers are expected to show little change, and thus are not good biomarkers to monitor disease progression. Glucose hypometabolism as measured by FDG PET and CSF tau are supposed to be measures of synaptic dysfunction and neurodegeneration, respectively. These biomarkers will become abnormal somewhat later in the pre-clinical phase, and have a quite linear rate of change as cognitive function declines in the MCI phase. Structural MRI is thought to have a quite similar temporal course, but probably become abnormal even later in the pre-clinical phase. Structural MRI is a measure of atrophy as a result of neuronal death, and is expected to correspond well with the clinical expression of the disease.

The results in the studies reviewed here are not contradictory to this model. This might also be expected, as the model is emerged from several of these and other studies. This model is evidently incorporated in the revised diagnostic criteria for AD of the U.S. National Institute on Aging (4), and it seems probable that this will prepare for the clinical use of biomarkers in the diagnostics of AD in the future. But for the time being there is a need of additional studies to confirm the hypothesis in the model. Additional biomarker comparison studies over longer time intervals and post-mortem assessments of the amyloid tracers will bring further clarity. Also standards for application of the biomarkers must be developed, and cut-off values defining normal versus abnormal must be established before employment in clinical settings. The large on-going multi-center studies will probably account for the greater part of this research.

Clinical use of PET in early AD will also be depending on availability of PET centers and be an issue of costs. The new amyloid 18F-labelled tracers enhances the feasibility of amyloid imaging at smaller PET centers, because with their longer half-life compared to PiB, an on-site cyclotron will not be necessary.

Lastly, there is also an ethical dimension in the clinical use of early biomarkers. As long as no treatment can reverse or stop the neurodegenerative process, it is probable not desirable to receive the diagnosis long before symptoms occur. Hopefully, such drugs will eventually come, and intervention will be more effective in an early phase, before irreversible neuronal damage has happened. Having the necessary diagnostic methods to correctly identify AD at a prodromal stage will then be of vast significance for the individuals affected, but also be of importance for the society as a whole, possibly reducing the number of elderly in need of institutional care.

Abbreviations

Aβ	Amyloid β
APP	amyloid precursor protein
CERAD	Consortium to establish a registry of Alzheimer's disease
AD	Alzheimer's disease
DTI	Diffusion tensor imaging
DLB	Dementia with Lewy bodies
DLBD	Diffuse Lewy body disease
FDG	[^{18}F]Fluorodeoxyglucose
fMRI	Functional magnetic resonance imaging
FTD	Frontotemporal dementia
LBD	Lewy body dementia
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
PCA	Principal component analysis
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PIB	[^{11}C]Pittsburgh compound B
ROI	Region of interest
SPM	Statistical parametric mapping
VBA	Voxelbased analysis

Reference List

(1) Hjort PF, Waaler HTh. Demens frem mot 2050. Tidsskr Nor Legeforen 2010 Jul 1;2010(130):1356-8.

(2) Mattson MP. Pathways towards and away from Alzheimer's disease. Nature 2004 Aug 5;430(7000):631-9.

(3) Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet 2011 Mar 19;377(9770):1019-31.

(4) Jack CR, Jr., Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011 May;7(3):257-62.

(5) Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007 Aug;6(8):734-46.

(6) Williams R. Biomarkers: warning signs. Nature 2011 Jul 14;475(7355):S5-S7.

(7) Drzezga A. Concept of functional imaging of memory decline in Alzheimer's disease. Methods 2008 Apr;44(4):304-14.

(8) Herholz K, Ebmeier K. Clinical amyloid imaging in Alzheimer's disease. Lancet Neurol 2011 Jul;10(7):667-70.

(9) Mosconi L, Berti V, Glodzik L, Pupi A, De SS, de Leon MJ. Pre-clinical detection of Alzheimer's disease using FDG-PET, with or without amyloid imaging. J Alzheimers Dis 2010;20(3):843-54.

(10) Herholz K. Cerebral glucose metabolism in preclinical and prodromal Alzheimer's disease. Expert Rev Neurother 2010 Nov;10(11):1667-73.

(11) Langbaum JB, Chen K, Lee W, Reschke C, Bandy D, Fleisher AS, et al. Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Neuroimage 2009 May 1;45(4):1107-16.

(12) Durand-Martel P, Tremblay D, Brodeur C, Paquet N. Autopsy as gold standard in FDG-PET studies in dementia. Can J Neurol Sci 2010 May;37(3):336-42.

(13) Silverman DH, Small GW, Chang CY, Lu CS, Kung De Aburto MA, Chen W, et al. Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome. JAMA 2001 Nov 7;286(17):2120-7.

(14) Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain 2007 Oct;130(Pt 10):2616-35.

(15) Jagust W, Reed B, Mungas D, Ellis W, Decarli C. What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? Neurology 2007 Aug 28;69(9):871-7.

(16) Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. Ann Neurol 2001 Sep;50(3):358-65.

(17) Hoffman JM, Welsh-Bohmer KA, Hanson M, Crain B, Hulette C, Earl N, et al. FDG PET imaging in patients with pathologically verified dementia. J Nucl Med 2000 Nov;41(11):1920-8.

(18) Mosconi L, Mistur R, Switalski R, Tsui WH, Glodzik L, Li Y, et al. FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease. Eur J Nucl Med Mol Imaging 2009 May;36(5):811-22.

(19) Schöll M, Almkvist O, Bogdanovic N, Wall A, Langstrom B, Viitanen M, et al. Time course of glucose metabolism in relation to cognitive performance and postmortem neuropathology in Met146Val PSEN1 mutation carriers. J Alzheimers Dis 2011;24(3):495-506.

(20) Jagust WJ, Bandy D, Chen K, Foster NL, Landau SM, Mathis CA, et al. The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. Alzheimers Dement 2010 May;6(3):221-9.

(21) Landau SM, Harvey D, Madison CM, Reiman EM, Foster NL, Aisen PS, et al. Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 2010 Jul 20;75(3):230-8.

(22) Landau SM, Harvey D, Madison CM, Koeppe RA, Reiman EM, Foster NL, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. Neurobiol Aging 2011 Jul;32(7):1207-18.

(23) Walhovd KB, Fjell AM, Brewer J, McEvoy LK, Fennema-Notestine C, Hagler DJ, Jr., et al. Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer disease. AJNR Am J Neuroradiol 2010 Feb;31(2):347-54.

(24) Herholz K, Westwood S, Haense C, Dunn G. Evaluation of a calibrated (18)F-FDG PET score as a biomarker for progression in Alzheimer disease and mild cognitive impairment. J Nucl Med 2011 Aug;52(8):1218-26.

(25) Mosconi L, De SS, Li J, Tsui WH, Li Y, Boppana M, et al. Hippocampal hypometabolism predicts cognitive decline from normal aging. Neurobiol Aging 2008 May;29(5):676-92.

(26) Anchisi D, Borroni B, Franceschi M, Kerrouche N, Kalbe E, Beuthien-Beumann B, et al. Heterogeneity of brain glucose metabolism in mild cognitive impairment and clinical progression to Alzheimer disease. Arch Neurol 2005 Nov;62(11):1728-33.

(27) Nobili F, Salmaso D, Morbelli S, Girtler N, Piccardo A, Brugnolo A, et al. Principal component analysis of FDG PET in amnestic MCI. Eur J Nucl Med Mol Imaging 2008 Dec;35(12):2191-202.

(28) Drzezga A, Grimmer T, Riemenschneider M, Lautenschlager N, Siebner H, Alexopoulus P, et al. Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. J Nucl Med 2005 Oct;46(10):1625-32.

(29) Pagani M, Dessi B, Morbelli S, Brugnolo A, Salmaso D, Piccini A, et al. MCI patients declining and not-declining at mid-term follow-up: FDG-PET findings. Curr Alzheimer Res 2010 Jun;7(4):287-94.

(30) Clerici F, Del SA, Chiti A, Maggiore L, Lecchi M, Pomati S, et al. Differences in hippocampal metabolism between amnestic and non-amnestic MCI subjects: automated FDG-PET image analysis. Q J Nucl Med Mol Imaging 2009 Dec;53(6):646-57.

(31) Kim SH, Seo SW, Yoon DS, Chin J, Lee BH, Cheong HK, et al. Comparison of neuropsychological and FDG-PET findings between early- versus late-onset mild cognitive impairment: A five-year longitudinal study. Dement Geriatr Cogn Disord 2010;29(3):213-23.

(32) Mitchell AJ, Shiri-Feshki M. Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis. J Neurol Neurosurg Psychiatry 2008 Dec;79(12):1386-91.

(33) Wolk DA, Klunk W. Update on amyloid imaging: from healthy aging to Alzheimer's disease. Curr Neurol Neurosci Rep 2009 Sep;9(5):345-52.

(34) Ewers M, Sperling RA, Klunk WE, Weiner MW, Hampel H. Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. Trends Neurosci 2011 Aug;34(8):430-42.

(35) Quigley H, Colloby SJ, O'Brien JT. PET imaging of brain amyloid in dementia: a review. Int J Geriatr Psychiatry 2010 Dec 28.

(36) Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging 2010 Aug;31(8):1275-83.

(37) Chetelat G, Villemagne VL, Pike KE, Ellis KA, Bourgeat P, Jones G, et al. Independent contribution of temporal beta-amyloid deposition to memory decline in the pre-dementia phase of Alzheimer's disease. Brain 2011 Mar;134(Pt 3):798-807.

(38) Sojkova J, Driscoll I, Iacono D, Zhou Y, Codispoti KE, Kraut MA, et al. In vivo fibrillar beta-amyloid detected using [11C]PiB positron emission tomography and neuropathologic assessment in older adults. Arch Neurol 2011 Feb;68(2):232-40.

(39) Cairns NJ, Ikonomovic MD, Benzinger T, Storandt M, Fagan AM, Shah AR, et al. Absence of Pittsburgh compound B detection of cerebral amyloid beta in a patient with clinical, cognitive, and cerebrospinal fluid markers of Alzheimer disease: a case report. Arch Neurol 2009 Dec;66(12):1557-62.

(40) Ikonomovic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain 2008 Jun;131(Pt 6):1630-45.

(41) Bacskai BJ, Frosch MP, Freeman SH, Raymond SB, Augustinack JC, Johnson KA, et al. Molecular imaging with Pittsburgh Compound B confirmed at autopsy: a case report. Arch Neurol 2007 Mar;64(3):431-4.

(42) Villemagne VL, Pike KE, Chetelat G, Ellis KA, Mulligan RS, Bourgeat P, et al. Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease. Ann Neurol 2011 Jan;69(1):181-92.

(43) Jack CR, Jr., Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. Brain 2009 May;132(Pt 5):1355-65.

(44) Koivunen J, Scheinin N, Virta JR, Aalto S, Vahlberg T, Nagren K, et al. Amyloid PET imaging in patients with mild cognitive impairment: a 2-year follow-up study. Neurology 2011 Mar 22;76(12):1085-90.

(45) Okello A, Koivunen J, Edison P, Archer HA, Turkheimer FE, Nagren K, et al. Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. Neurology 2009 Sep 8;73(10):754-60.

(46) Wolk DA, Price JC, Saxton JA, Snitz BE, James JA, Lopez OL, et al. Amyloid imaging in mild cognitive impairment subtypes. Ann Neurol 2009 May;65(5):557-68.

(47) Forsberg A, Engler H, Almkvist O, Blomquist G, Hagman G, Wall A, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol Aging 2008 Oct;29(10):1456-65.

(48) Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011 Jan 19;305(3):275-83.

(49) Carome M, Wolfe S. Florbetapir-PET imaging and postmortem beta-amyloid pathology. JAMA 2011 May 11;305(18):1857-8.

(50) FDA advisory comittee briefing document: Peripheral and Central Nervous Systems Drugs Advisory Comittee. Food and Drug Administration 2010 December 20 [cited 2011 Sep 26];Available from: URL: http://www.fda.gov/downloads/AdvisoryComittees/ComitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryComittee/UCM240265.pdf

(51) Doraiswamy PM, Clark C, Sperling R, Reiman E, Pontecorvo M, Sabbagh M, et al. Prognostic significance of florbetapir F18 PET imaging in MCI and mormal elderly: Final results from a longitudinal multicenter trial. Alzheimer's & dementia : the journal of the Alzheimer's Association 7[4], S108. 1-7-2011.
Ref Type: Abstract

(52) Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura P, Ayutyanont N, et al. Using Positron Emission Tomography and Florbetapir F 18 to Image Cortical Amyloid in Patients With Mild Cognitive Impairment or Dementia Due to Alzheimer Disease. Arch Neurol 2011 Jul 11.

(53) Villemagne VL, Ong K, Mulligan RS, Holl G, Pejoska S, Jones G, et al. Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. J Nucl Med 2011 Aug;52(8):1210-7.

(54) Barthel H, Gertz HJ, Dresel S, Peters O, Bartenstein P, Buerger K, et al. Cerebral amyloid-beta PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. Lancet Neurol 2011 May;10(5):424-35.

(55) Bayer. Phase III study of florbetaben(BAY94-9172) PET imaging for detection/exclusion of cerebral β-amyloid compared to histopathology - NCT01020838. ClinicalTrials gov 2011 September 16 [cited 2011 Sep 28];Available from: URL: http://clinicaltrials.gov/ct2/show/NCT01020838

(56) Ong K, Villemagne V, Bahar-Fuchs A, Lamb F, Chetelat G, Reininger C, et al. Conversion from mild cognitive impairment to Alzheimer's disease over 12 months: Predictive value of AÎ² imaging with 18F-Florbetaben. Alzheimer's & dementia : the journal of the Alzheimer's Association 7[4], S33. 1-7-2011.
Ref Type: Abstract

(57) Vandenberghe R, Van LK, Ivanoiu A, Salmon E, Bastin C, Triau E, et al. 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. Ann Neurol 2010 Sep;68(3):319-29.

(58) Wolk DA, Grachev ID, Buckley C, Kazi H, Grady MS, Trojanowski JQ, et al. Association Between In Vivo Fluorine 18-Labeled Flutemetamol Amyloid Positron Emission Tomography Imaging and In Vivo Cerebral Cortical Histopathology. Arch Neurol 2011 Jul 11.

(59) Villemagne VL, Rowe CC. Amyloid imaging. Int Psychogeriatr 2011 Jun 10;1-9.

(60) Small GW, Kepe V, Ercoli LM, Siddarth P, Bookheimer SY, Miller KJ, et al. PET of brain amyloid and tau in mild cognitive impairment. N Engl J Med 2006 Dec 21;355(25):2652-63.

(61) Tolboom N, Yaqub M, van der Flier WM, Boellaard R, Luurtsema G, Windhorst AD, et al. Detection of Alzheimer pathology in vivo using both 11C-PIB and 18F-FDDNP PET. J Nucl Med 2009 Feb;50(2):191-7.

(62) Nordberg A, Rinne JO, Kadir A, Langstrom B. The use of PET in Alzheimer disease. Nat Rev Neurol 2010 Feb;6(2):78-87.

(63) Jack CR, Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010 Jan;9(1):119-28.

(64) Förster S, Grimmer T, Miederer I, Henriksen G, Yousefi BH, Graner P, et al. Regional Expansion of Hypometabolism in Alzheimer's Disease Follows Amyloid Deposition with Temporal Delay. Biol Psychiatry 2011 Jun 14.

(65) Misra C, Fan Y, Davatzikos C. Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. Neuroimage 2009 Feb 15;44(4):1415-22.

(66) Ewers M, Walsh C, Trojanowski JQ, Shaw LM, Petersen RC, Jack CR, Jr., et al. Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. Neurobiol Aging 2010 Dec 13.

(67) Grambaite R, Reinvang I, Selnes P, Fjell AM, Walhovd KB, Stenset V, et al. Pre-dementia memory impairment is associated with white matter tract affection. J Int Neuropsychol Soc 2011 Jan;17(1):143-53.

(68) Fellgiebel A, Dellani PR, Greverus D, Scheurich A, Stoeter P, Muller MJ. Predicting conversion to dementia in mild cognitive impairment by volumetric and diffusivity measurements of the hippocampus. Psychiatry Res 2006 Apr 30;146(3):283-7.

(69) Teipel SJ, Meindl T, Wagner M, Stieltjes B, Reuter S, Hauenstein KH, et al. Longitudinal changes in fiber tract integrity in healthy aging and mild cognitive impairment: a DTI follow-up study. J Alzheimers Dis 2010;22(2):507-22.

(70) Petrella JR, Sheldon FC, Prince SE, Calhoun VD, Doraiswamy PM. Default mode network connectivity in stable vs progressive mild cognitive impairment. Neurology 2011 Feb 8;76(6):511-7.

(71) Walhovd KB, Fjell AM, Amlien I, Grambaite R, Stenset V, Bjornerud A, et al. Multimodal imaging in mild cognitive impairment: Metabolism, morphometry and diffusion of the temporal-parietal memory network. Neuroimage 2009 Mar 1;45(1):215-23.

(72) Hinrichs C, Singh V, Xu G, Johnson SC. Predictive markers for AD in a multi-modality framework: an analysis of MCI progression in the ADNI population. Neuroimage 2011 Mar 15;55(2):574-89.

(73) Zhang D, Wang Y, Zhou L, Yuan H, Shen D. Multimodal classification of Alzheimer's disease and mild cognitive impairment. Neuroimage 2011 Apr 1;55(3):856-67.

Appendix

Study		Biomarker	N a+b+c+d	True pos a	False pos b	False neg c	True neg d	# AD a+c	# Not AD b+d	# Pos a+b	# Neg c+d	Acc . (a+d)/ (a+b+c+d)	Sens. a/(a+c)	Spec. d/(b+d)	PPV a/(a+b)	NPV d/(c+d)
Silverman (13)	Table 1	FDG PET	138	91	11	6	30	97	41	102	36	88 %	94 %	73 %	89 %	83 %
Foster (14)	Table 1	FDG PET	45	30	10	1	4	31	14	40	5	89 %	98 %	73 %	88 %	91 %
Jagust (15)	Table 1	FDG PET	44	21	5	4	14	25	19	26	18	80 %	84 %	74 %	81 %	78 %
Minoshima (16)	Table 1	FDG PET	21	9	2	1	9	10	11	11	10	86 %	90 %	80 %	82 %	90 %
Hoffman (17)	Table 1	FDG PET	19	11	2	2	4	13	6	13	6	79 %	85 %	67 %	85 %	67 %
Landau (21)	Table 2,3	FDG PET	85	21	30	7	27	28	57	51	34	56 %	75 %	47 %	41 %	79 %
Landau (21)	Table 2	MRI hipp.vol	85	20	29	8	28	28	57	49	36	56 %	71 %	49 %	41 %	78 %
Landau (21)	Table 2	CSF $A\beta_{1-42}$	85	21	35	7	22	28	57	56	29	51 %	75 %	39 %	38 %	76 %
Landau (21)	Table 2	AVLT ep.mem.	85	25	36	3	21	28	57	61	24	54 %	89 %	37 %	41 %	88 %
Landau (21)	Table 2	ApoE ε4	85	17	25	11	32	28	57	42	43	58 %	61 %	56 %	40 %	74 %
Herholz (24)	Table 3	FDG PET	94	17	21	13	43	30	64	38	56	64 %	57 %	67 %	45 %	77 %
Anchisi (26)	Table 3	FDG PET	48	13	6	1	28	14	34	19	29	85 %	93 %	82 %	68 %	97 %
Nobili (27)	Table 3	FDG PET	33	9	2	2	20	11	22	11	22	88 %	82 %	91 %	82 %	91 %
Drzezga (28)	Table 3	FDG PET	30	11	2	1	16	12	18	13	17	90 %	92 %	89 %	85 %	94 %
Villemagne (42)	Table 4	PiB PET	65	30	15	1	19	31	34	45	20	75 %	97 %	56 %	67 %	95 %
Okello (45)	Table 4	PiB PET	31	14	3	1	13	15	16	17	14	87 %	93 %	81 %	82 %	93 %
Koivunen (44)	Table 4	PiB PET	29	16	5	1	7	17	12	21	8	79 %	94 %	58 %	76 %	88 %
Wolk (46)	Table 4	PiB PET	23	5	8	0	10	5	18	13	10	65 %	100 %	56 %	38 %	100 %
Forsberg (47)	Table 4	PiB PET	21	7	4	0	10	7	14	11	10	81 %	100 %	71 %	64 %	100 %
Ewers (66)	Sect. 4.2	MRI entorhin.	130					58	72			69 %	53 %	77 %		
Ewers (66)	Sect. 4.2	Comb.	130					58	72			76 %	88 %	68 %		
Zhang (73)	Sect. 4.3	Comb.	99	39	15	4	41	43	56	54	45	81 %	91 %	73 %	72 %	91 %

Numbers are collected from article

Numbers are calculated from data in article